REMARKS

This Reply is responsive to the Office Action dated October 14, 1999. Entry of the foregoing, examination and reconsideration of the above-identified application pursuant to 37 CFR §1.112 are respectfully requested.

By the present amendment, applicants have amended the specification on page 30 with the appropriate SEQ ID NOs as requested in the Office Action. In addition, applicants have replaced the first paper copy of the sequence listing with a corrected version as required in the Notice to Comply with the Sequence Rules attached to the Office Action. A corrected diskette is also attached hereto, along with a declaration by applicant's agent that the computer readable form and the paper copy are the same and contain no new matter.

The claims have been amended to change "without regard to a wild type sequence" to "wherein said population is synthesized without reference to a wild type sequence" in order to clarify the nature of the claimed invention, and to emphasize that this phrase refers to the manner in which the nucleotide populations are generated, not the populations themselves. This amendment and the rejection under 35 U.S.C. §112, second paragraph regarding the original phraseology are discussed further below.

In addition, claims 7 and 12 have been amended to clarify that the noted frequency of stop codons is reduced as compared to codons encoding amino acids as suggested in the Office Action at the top of page 5. Claims 14 and 24 have also been amended as suggested in the Office Action in order to resolve allegedly unclear phraseology, and Claim 22 has been

amended to refer to about a billion "or more" nucleotide sequences to retain consistency with claim 24 as presented in the Preliminary Amendment filed June 9, 1999 and amended herein.

In addition, claims 26 and 27 have been added for the purposes of the requested interference, and are substantially the same as claims 1 and 2 of Kauffman U.S. Patent 5,976,862, which issued on November 2, 1999. Support for these claims in both the present specification and in parent application 06/887,070 is provided in Appendix C. No new matter has been added.

Turning now to the Office Action, the Specification has been objected to because the CRF Diskette submitted previously was not in compliance. According to the Problem Report, this was because the <223> explanation required for undefined nucleotides in SEQ ID NO: 15 did not refer to all the undefined nucleotides present in the defined sequence. Both the paper copy and the diskette have been corrected and the appropriate amendments to replace the prior sequence listing are presented above. Withdrawal of the objection is respectfully requested.

The Specification was also objected to because several sequences on page 30 of the specification were not labeled with the appropriate SEQ ID NO. This oversight has also been corrected above by amending the specification to include reference to two SEQ ID NOs at the appropriate positions. Applicants further note that the sequences disclosed on page 30, on lines 13 and 20, do not qualify as nucleotide sequences subject to the Sequence Rules according to 37 CFR 1.821(a) because they are less than ten nucleotides long. Therefore,

these sequences have not been labeled nor included in the sequence listing. Applicants believe that the application is now compliant with 37 CFR §§ 1.821-1.825, and withdrawal of the objection to the specification is respectfully requested.

Several claims were rejected under 35 U.S.C. §112, second paragraph for lack of clarity. These rejections are addressed in the order presented in the Office Action beginning on page 4. First, claims 3, 4, 6 and 13-25 were rejected because it was allegedly unclear how the phrase "without regard to a wild type sequence" limits the claimed nucleotide sequences. Applicant respectfully submits that the noted phrase limits the manner in which the nucleotide sequences are produced, not the nucleotide sequences themselves. Indeed, as discussed in the Preliminary Amendment submitted on June 9, 1999, by using this phrase applicant sought to emphasize the fact that the random sequences of the present invention contain no bias toward wild type, as was seen in typical mutagenesis experiments known in the art at the time the present invention was made, and that no knowledge regarding the sequence or structure of wild type proteins is required for the claimed methods. This means that, although wild type sequences may be present in the random populations used in the present invention, the populations as a whole are generated randomly with no reference to any wild type sequence. The claims have been amended above to emphasize this point where it may not have been clear. Therefore, withdrawal of the rejection under 35 U.S.C. § 112, second paragraph as it pertains to these particular claims is respectfully requested.

Claim 7 was rejected under 35 U.S.C. § 112, second paragraph for allegedly omitting

essential steps. According to the Office Action, the claim omits a step pertaining to the identification of sequences which provide a desired biological activity. Applicants respectfully disagree with the rejection. According to the preamble of claim 7, the claim is directed to a method of producing a mixed population of random nucleotide sequences, not a method of identifying a sequence which provides a biological activity (although the preamble does specify that this is an underlying motivation for producing the random population).

Furthermore, Applicants respectfully note that the claims of the present application were submitted for the purpose of initiating an interference between the instant application and the Kauffman U.S. Patents and Applications as discussed in the Preliminary Amendment and Request for Interference filed June 9, 1999. Claim 7 in particular was modeled after claim 34 of Kauffman Patent 5,723,323, except uses the language particular to applicant's own specification. Claim 34 of Kauffman is directed to a method of "producing a diverse population of stochastically generated polynucleotide sequences encoding a diverse population of ligand binding peptides, polypeptides or proteins . . .," but has no process step whereby such peptides, polypeptides and proteins are identified. Thus, the Examiner should withdraw the rejection of instant claim 7 unless the Examiner is prepared to say that such a claim is unpatentable to anyone, a rejection that requires approval of the group director in view of the patenting of claim 34 of Kauffman 5,723,323. Because Applicants have support for such a claim in their specification and are attempting to initiate interference proceedings, withdrawal of the rejection under 35 U.S.C. § 112, second as it pertains to claim 7 in this instance is

respectfully requested.

Claim 7 was also rejected, as was claim 12, for including the phrase "the frequency of stop codons in said mixed population is reduced" without some qualifying description to evaluate what "reduced" means. These claims were amended above as suggested in the Office Action at the top of page 5, therefore withdrawal of the rejection is respectfully requested.

Claim 14 was rejected for including the phrase "capable of." Claim 14 has been amended above by deletion of this phrase, therefore withdrawal of the rejection is respectfully requested.

Claim 24 was rejected for including the phrase "greater about a billion." This grammatical oversight has been corrected above and withdrawal of the rejection is respectfully requested.

Next, Claims 3, 4, 6, 13-18 and 21-25 were rejected under 35 U.S.C. § 102(e) as being allegedly anticipated by Pieczenik (US Patent 5,866,363). It is the Examiner's opinion that the Declaration pursuant to 37 CFR § 1.131 filed on September 24, 1999 is ineffective to overcome Pieczenik because Pieczenik allegedly claims the same invention as the present application. Accordingly, it is the Examiner's opinion that Pieczenik should also be a party in the requested interference, and that applicants should take appropriate steps to modify the indicated parties.

As explained in the Reply to Examiner Interview filed September 24, 1999, it is applicant's opinion that Pieczenik should not be included in the Interference because the

Pieczenik claims are directed to a potentially separately patentable species within the broader genus defined by the claims of the instant application and the Kauffman patents and applications. Moreover, the Pieczenik claims are only entitled to the filing date of the Pieczenik CIP application (February 28, 1991).

For instance, while the present invention is directed to screening random nucleic acids and peptides in general for a variety of desired biological functions, Pieczenik concerns only the screening of short random peptide populations (4 to 12 amino acids) specifically for antigenic epitopes using a particular expression system, a filamentous phage vector. The filamentous phage vector system disclosed in Pieczenik is required for the practice of Pieczenik's methods, because without such a vector system for expressing random peptides on the surface of host cells, the cells would need to be lysed (for instance by lytic phage infection, i.e., λgt11 infection, also disclosed in Pieczenik) in order to detect the random peptides using the antibodies of interest. The problem, however, is that once the cells are lysed all cellular proteins are exposed or released, and it would be extremely difficult if not impossible to identify antibodies that specifically bind to random peptides and not other cellular proteins. Use of a filamentous phage vector system was not specifically disclosed until the Pieczenik CIP application was filed on February 28, 1991. Because this vector system is required to practice Pieczenik's methods, Pieczenik does not satisfy the requirements of 35 U.S.C. § 112, first paragraph until 1991 and is therefore only entitled to benefit of the CIP filing date.

While not agreeing with the Examiner that Pieczenik should be included in the

interference for the reasons provided above and discussed at length in the Reply to the Examiner Interview filed September 24, 1999, applicants have modified the original Request for Interference filed June 9, 1999 to include Pieczenik given that the Examiner still believes that Pieczenik is directed to the same patentable invention.[1] The inclusion of Pieczenik in the Renewed Request for Interference has therefore been made solely in order to expedite the proceedings, and applicants reserve the right to challenge the inclusion of Pieczenik as a party during the interference.

Applicants note that another Kauffman patent (US 5,976,862) has issued since the original Request for Interference was filed, therefore, the Renewed Request for Interference includes reference to this recent Kauffman patent as well.

Finally, claims 3, 4, 6, 13 and 15-25 were rejected as being allegedly unpatentable over claims 2 and 3 of U.S. Patent No. 5,824,469 under the judicially created doctrine of obvious-type double patenting. A terminal disclaimer is attached hereto, thereby rendering this rejection moot.

Applicant respectfully submits that all rejections presented in the Office have now been addressed and resolved either by comment or amendment. Accordingly, Applicants

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[1] Applicants note that, assuming Pieczenik is directed to the same patentable invention as to be included in the interference, a Declaration pursuant to 37 CFR § 1.608(b) should not be required because Pieczenik is only entitled to the filing date of the CIP application 07/662,764 (February 28, 1991). However, should the Examiner or Board decide that such a Declaration is required, Applicants are prepared to submit this Declaration as well as other affidavit evidence if required.

respectfully request that the necessary interference now be declared. Applicant presents the instant Reply in conjunction with a Renewed Request for Interference Pursuant to §§ 1.604 and 1.607 which begins on the following page. Appendix B to the initial Request filed June 9, 1999 is still applicable for support to claims 3, 4, 6-8 and 11-25 because the amendments presented herein were not substantive and introduced no new matter. Appendix C attached hereto provides support for newly added claims 26 and 27. The information required by 37 C.F.R. §§ 1.604(a) and 1.607(a) is again set forth under headings below which correspond to the subsections of §§ 1.604(a) and 1.607(a) to facilitate consideration by the Examiner. Because applicant's effective filing date, July 17, 1986, is earlier than the effective filing date of the patents identified herein (November 20, 1986 for Kauffman and February 28, 1991 for Pieczenik), the present applicants should be declared the senior party.[2]

Horwitz should be designated the senior party in the interference. The earliest effective filing date of Kauffman for the '192 patent is November 20, 1986, while Horwitz has an effective filing date of July 17, 1986. With respect to the effective filing dates of the other Kauffman patents, and particularly the '483, '476 and '862 patents, MPEP 2308.01 makes it clear that foreign priority under 35 U.S.C. 119 should not be taken into account in determining effective filing dates. Thus, the Kauffman claim for the benefit of the Swiss application should not be taken into account in determining senior party status. Similarly, with regard to the Kauffman '323 and '514 patents, the filing date of the Kauffman PCT application, PCT/CH85/00099, should not be taken into account, but rather the 35 U.S.C. 102(e) date of the PCT application (November 20, 1986) because that is the date that it would be a reference against the Horwitz claims as discussed in MPEP 2308.01. The effective filing date of Pieczenik is February 28, 1991 as discussed above in footnote 2.

I. IDENTIFICATION OF THE PATENTS AND APPLICATIONS WHICH INCLUDE SUBJECT MATTER WHICH INTERFERES WITH THE INSTANT APPLICATION

Pursuant to 37 CFR §1.607(a)(1), Applicants request that an interference be declared between the instant application and U.S. Patent Nos. 5,723,323 (the '323 patent), 5,763,192 (the '192 patent), 5,817,483 (the '483 patent), 5,824,514 (the '514 patent), 5,814,476 (the '476 patent), and 5,976,862 (the '862 patent) of Kauffman et al., as well as U.S. Patent 5,866,363 (the '363 patent) of Pieczenik if required.

Pursuant to 37 CFR §1.604(a)(2), the patent applications which are believed to claim subject matter which interferes with subject matter claimed in the present application ("the Kauffman applications") are U.S. Application Serial No. 08/468,468, filed on June 5, 1995, and U.S. Application Serial No. 08/464,569, filed on June 5, 1995.[3]

II. PRESENTATION OF PROPOSED COUNT

Attached Appendix A sets forth a proposed Count pursuant to 37 CFR §§ 1.607(a)(2) and 1.604(a)(1). The proposed Count is an alternative Count prepared after consideration of the subject matter claimed by the respective parties. Because applicants believe that Pieczenik should not be included in the Interference as discussed in Section V of this Request, a separate alternative Count is set forth in Appendix B and includes only subject matter pertaining to

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[3] Applicants note that U.S. Application Serial No. 08/464,327 of Kauffman, which was mentioned in the original Request for Interference, issued as U.S. Patent No. 5,976,862, now mentioned herein pursuant to 37 CFR § 1.607.

Kauffman and the instant application.[4]

Proposed Count A is at least as broad as the claims of the six Kauffman Patents and the claims of Pieczenik in that the independent claims of these patents are presented in the alternative in addition to the claims of the present application. The independent claims of the Kauffman patents include claims 1, 15, 16, 24, 25, 34, 41-45 of the '323 patent, claim 1 of the '192 patent, claims 1-4, 6, 17, 29, 35, and 36 of the '483 patent, claims 1, 11, 12, 18, 27 and 37 of the '514 patent, claims 1-3, 8, 15, 29, 47, 61, 79, 91 and 103 of the '476 patent, claims 1-3, 9, 17 and 26 of the '862 patent, and the independent claims of Pieczenik include claims 1, 10, 23, 24, 34, 47, 67, 77 and 90 of the Pieczenik '363 patent.

Because applicants do not have access to the claims of the putative pending Kauffman applications, applicants were not able to copy these claims. However, it is very likely that the claims of any pending related application should also be included in the interference, given the fact that all the claims in the six issued Kauffman patents are directed to the same patentable invention as disclosed and claimed in the present application. The Examiner is respectfully requested to review any related pending Kauffman applications and any related Pieczenik

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The second proposed Count (presented in Appendix B) includes the independent claims from the first five Kauffman patents as presented in the previously proposed Count in the original Request for Interference on June 9, 1999 (attached to that paper as Appendix A), and also includes subject matter pertaining to the newly issued Kauffman '862 patent, as well as the claims of the present application, which were inadvertently omitted from the previously proposed Count. The proposed Count presented in Appendix A attached hereto includes all the material included in Appendix B, as well as the independent claims from Pieczenik presented in the alternative.

applications as to whether such applications contain claims which are directed to the same patentable invention as defined by those discussed herein, and determine whether such application or applications should be included in the interference. If necessary, the Examiner is respectfully requested to suggest a claim to applicants corresponding to the claims in any pending application pursuant to 37 CFR 1.605(a) so that all related applications may be included in the interference, and amend the proposed Count.

An alternative Count which includes the Kauffman independent claims, the Pieczenik independent claims and claims identical to the corresponding claims of the instant application is being proposed in part because of the different language utilized by the respective parties to describe the same patentable invention.[5]

III. IDENTIFICATION OF CLAIMS OF THE KAUFFMAN PATENTS WHICH CORRESPOND TO THE PROPOSED COUNT PURSUANT TO 37 CFR § 1.607(a)(3)

Claims 1-48 of the Kauffman '323 Patent define the same patentable invention as claims 1-5 of the Kauffman '192 Patent and as claims 1-53 of the Kauffman '483 Patent and as claims 1-46 of the Kauffman '514 Patent and as claims 1-107 of the Kauffman '476 Patent. These claims correspond to and define the same patentable invention as claims 3, 4, 6-8 and 11-25 of

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[5] The phrase "same patentable invention" is used herein in the context of 37 CFR §1.601(n) to indicate that the inventions are the same or obvious in view of each other and should therefore be involved in an interference. The phrase should not be taken as an admission that any particular Kauffman claim is patentable under 35 U.S.C. §§ 102, 103 or 112.

the instant Horwitz application (and allegedly the same patentable invention as claims 1-92 of Pieczenik according to the Office Action).

All the claims are essentially directed to or based on methods of searching for biologically active nucleotide sequences from among a randomly or stochastically generated population, on the theory that particular novel sequences capable of predetermined or desired biological functions may be identified.[6] The crux of the invention reflected in all the claims rests on the discovery, which was indeed a "leap of faith" at the time the present invention was made, that randomly generated sequences could perform specific biological functions in the absence of millions of years of evolutionary refinement. While many of the claims in the various patents and applications included in this Request incorporate additional steps beyond the generation and screening of or selecting for randomly generated sequences having a particular function, such steps do not make a patentable difference when considering the state of the art at the time.[7]

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[6] Although it is not clear what the term "stochastic" means, applicants assume it has the same meaning as "random" as used in the present application. This issue is discussed at length on pages 4-6 of the Reply to the Examiner Interview filed on September 24, 1999.

[7] Applicants also note that, although Pieczenik did not disclose use of the filamentous phage vector system until the CIP application was filed on February 28, 1991, the use of viral vectors to map antigenic determinants was known in the art much earlier. For instance, Pieczenik filed an Information Disclosure Statement on September 6, 1991, which included the Nunberg reference entitled "Method to map Antigenic Determinants Recognized by Monoclonal Antibodies: Localization of a Determinant of Virus Neutralization on Feline Leukemia Virus Envelope Protein gp70" (Proc. Natl. Acad. Sci. USA 81: 3675). This reference was published in 1984. Pieczenik distinguished his invention based on the length of the inserts containing the random nucleotides, which were much shorter and encoded only 4-12

Indeed, as will be discussed herein, it was known at the time that polynucleotides could be cloned into expression vectors, and that such vectors could be transformed into and amplified in an appropriate host cell. It was known that such a host cell could be analyzed, tested or selected based on whether it expressed the protein encoded by or displayed the function provided by the cloned nucleotide sequence. It was known that vector could then be isolated from identified transformed cells and the cloned nucleotide sequence could then be isolated from the vector using standard techniques in the art, i.e., restriction and gel purification. And it was known that such host cells could be used to produce the recombinant protein, which could be purified and used for whatever purpose it was sought, i.e., for vaccine development, as a drug, to raise antibodies, etc. Such manipulations of nucleic acids and standard recombinant techniques do not impart a patentable distinction to the novel premise at the time that a completely random population of nucleotides could generate a sequence having a particular biological activity.

Likewise, while many of the claims in the various Kauffman patents incorporate limitations which more precisely define the manner in which nucleotide sequences are generated, or the manner in which nucleotide sequences are screened, or the particular predetermined or desired property of the nucleotide sequence identified, these specific limitations are merely variations of the general concept, and apparent applications of the method, given the state of the art at the time.

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amino acids.

Indeed, it was known that nucleotide sequences could be synthesized chemically or by using enzymes like polymerase and terminal transferase. It was known that new nucleotide sequences could be generated by ligating smaller nucleotide sequences together. It was known that DNA could be cleaved with restriction enzymes and re-ligated using DNA ligase following hybridization of the "sticky ends" of the cleaved DNA. And it was also known that DNA could be ligated in the absence of complementary ends, i.e., blunt-end ligation.

Thus, while there are many claims which have issued in the six Kauffman patents, each merely rephrases the crux of the invention, or adds or specifies particular steps, which would have been apparent to a person skilled in the art when the basic novelty of the invention is taken in view of the state of the art. Therefore, all the claims of each Kauffman patent are believed to correspond to the Count pursuant to 37 CFR §1.607(a)(3) for the following reasons, with each patent discussed separately for the Examiner's convenience. A separate discussion of the Pieczenik '363 patent is included at the end of this section.

The Kauffman '323 Patent

The proposed Count includes Kauffman '323 claims 1, 15, 16, 24, 25, 34, 41-45 joined individually by "or" to each other and independent claims from the other five Kauffman patents.[8] Kauffman '323 claims 1, 15, 16, 24, 25, 34, 41-45 thus each correspond exactly to

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[8] The Count proposed in Appendix A also includes the independent claims from the Pieczenik '363 patent.

one part of the proposed Count. Because of the use of "or," correspondence to one part of the proposed Count is sufficient.

'323 claims 1-14

Thus, '323 claim 1 corresponds to the Count because it is included as an alternative part of the Count. However, it is noted that '323 claim 1 would also correspond to the Count in that it is obvious in view of '192 claim 1, which also corresponds exactly to the Count. '323 claim 1 differs from '192 claim 1 in that it defines the predetermined property of the peptide, polypeptide or protein as a "binding property to a ligand." However, such a property would have been an apparent application of the method recited in '192 claim 1, because it was known in the art at the time that cloned nucleotide sequences could be used to produce peptides, which could be identified by virtue of a binding property. See, i.e., Matteucci and Heyneker (1983) (attached), describing antibody screening of recombinant proteins; see also, the present application at page 7, lines 26-29, discussing enzyme and enzyme-substrate reactions as a method to screen for the presence of peptide.

Nevertheless, '323 claim 1 corresponds exactly to part of the Count. Claims 2-14 of the '323 patent all depend from '323 claim 1 and define the same patentable invention as '323 claim 1. '323 claims 2-14 therefore also correspond to the Count. For instance, claim 14 specifies that step (c) of claim 1 further comprises digesting the stochastic population of expression vectors with a restriction enzyme and religating the pieces to generate new

stochastic sequences. Such a step would have been an obvious extension of the method of '323 claim 1, because the fact that new sequences could be generated by ligating together restriction fragments was well-known in the art at the time the Kauffman application was filed. See, i.e., Shortle (1983), p. 184, describing the generation of new mutant genes by digesting with restriction enzymes and inserting restriction fragments.

'323 claims 15 and 42

Kauffman '323 claim 15 corresponds to the Count because it is included in the Count as discussed above. However, it is noted that '323 claim 15 is directed to an isolated, diverse population of peptides, polypeptides or proteins comprising greater than about 1 X 10^5 different stochastic amino acid sequences encoded by stochastic polynucleotide sequences. This claim is obvious in view of, at the very least '323 claim 1, which is directed to a method of identifying a peptide, polypeptide or protein from a diverse population of peptides, polypeptides or proteins expressed by host cells containing stochastically generated polynucleotide sequences. Once one has produced a population of peptides or proteins using recombinant DNA technology, one could have readily separated the peptides or proteins from the host cells to create an isolated population of diverse peptides, polypeptides or proteins using standard techniques known in the art, i.e., see Kauffman '323 col. 10, lines 13-31, discussing how purification of particular proteins and populations of proteins can be "carried out by established procedures." Hence, although '323 claim 15 corresponds to the Count

because it is part of the count, it also corresponds because it is obvious over '323 claim 1 in view of the state of the art at the time.

Similarly, '323 claim 42 corresponds to the Count because it is included as part of the Count. However, '323 claim 42 is also directed to an isolated, diverse population of peptides encoded by stochastic polynucleotide sequences (as is '323 claim 15), but specifies that the polynucleotide sequences are 300 nucleotides or less. Since limiting the length of the stochastic polynucleotide sequences would not alone present a patentable distinction, '323 claim 42 would also correspond to the Count in the same manner that claim 15 corresponds to the Count, since it is obvious in view of claim 1.

'323 claims 16-24 and 43

Kauffman '323 claim 16 corresponds exactly to part of the Count. Claims 17-23 all depend from '323 claim 16 and define the same patentable invention as '323 claim 16. '323 claims 17-23 therefore also correspond to the Count. While '323 claim 24 exactly corresponds to part of the Count, it is noted that '323 claim 24 is directed to an isolated, diverse population of polynucleotide sequences and would be obvious in view of claim 16, which recites a method of isolating a polynucleotide sequence following screening of host cells expressing stochastically generated polynucleotide sequences. If one could isolate a particular polynucleotide sequence from among a diverse, stochastic population, then isolating the population itself would be a clear variation, since methods for isolating a population of vectors

were known at the time the Kauffman was made. See, i.e., Maniatis et al. Molecular Cloning: A Laboratory Manual, Cold Spring Harbor, New York (1982), p. 2 (attached). '323 claim 24 therefore also corresponds to the Count, to the extent that it is obvious in view of claim 16 when viewed with the state of art at the time.

'323 claim 43 corresponds to the Count in the same manner that claim 24 corresponds to the Count. While claim 43 is included as part of the Count, since claim 43 is also directed to an isolated, diverse population of polynucleotide sequences which is only further defined by limiting the stochastically generated polynucleotide sequences to 300 or bases or less. Since limiting the length of the stochastic sequence does not impart a patentable distinction,[9] claim 43 would also be obvious in view of claim 16, and therefore also corresponds to the Count as an apparent variation of claim 16.

'323 claims 25-33

Kauffman '323 claim 25 corresponds exactly to part of the Count. Claims 26-33 all depend from '323 claim 25 and define the same patentable invention as '323 claim 25. '323 claims 26-33 therefore also correspond to the Count. For instance, '323 claim 30 specifies that

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[9] Although limiting the length of the stochastic or random sequence would not alone provide a patentable distinction when practicing the generic screening methods of the present invention, it is Applicant's position that the limitation of the short random sequences used in the methods of Pieczenik, combined with the particularly screening tools and methods and the intended goal render Pieczenik a separately patentable species. This will be discussed further in Section V of this Request.

the stochastically generated polynucleotide sequences of claim 25 are generated by "stochastic copolymerization." While the '323 specification does not make it clear what "stochastic polymerization" means, claims 95 and 96 of the '476 patent indicate that such "copolymerization can be accomplished by either hybridization of complementary sequences or by ligation." Ligation was certainly a well known technique for joining together segments of nucleic acids at the time the Kauffman application was filed. Hence, specifying that the stochastic polynucleotide sequences were generated by "stochastic copolymerization" does not provide a patentable distinction in view of the state of the art at the time. Thus, claim 30 would also correspond to the Count, because it is directed to the same patentable invention as claim 25.

Likewise, claim 33 specifies that step (c) of the method of claim 25 further comprises digesting the vectors with a restriction enzyme and religating the pieces to form a new different population. Ligating together restriction fragments to form new sequences was well known in the art at the time the Kauffman application was filed. See, Shortle (1983) (attached). Thus, claim 33 does not provide a patentable distinction over claim 25 when taken in view of the art, and would therefore also correspond to the Count.

'323 claims 34-41 and 44

'323 claim 34 corresponds exactly to part of the Count. Claims 35-40 all depend from '323 claim 34 and define the same patentable invention as '323 claim 34. '323 claims 35-40

therefore also correspond to the Count, in much the same manner as claims 26-33 correspond to the Count because they are dependent on claim 25.

'323 claim 41 is directed to an isolated, diverse population of vectors comprising stochastically generated polynucleotide sequences, and is obvious in view of, at the very least claim 34, which recites a method of producing stochastically generated polynucleotide sequences by inserting them into a population of vectors. While claim 41 corresponds to the Count because it is part of the Count, since techniques for cloning DNA sequences into vectors and methods for isolating vectors were well known techniques at the time the Kauffman application was filed, i.e., see Maniatis (1982), claim 41 is also obvious in view of claim 34, and therefore corresponds to the Count also because claim 34 is part of the Count.

'323 claim 44 would correspond to the Count in the same manner that claim 41 corresponds to the Count, since claim 44 is also directed to an isolated, diverse population of vectors which is only further defined by limiting the stochastically generated polynucleotide sequences to 300 or bases or less. So, although claim 44 corresponds to the Count because it is part of the Count, since limiting the length of the stochastic sequence does not alone impart a patentable distinction, claim 44 would also be obvious in view of claim 34, and therefore also corresponds to the Count in this manner.

Finally, claims 45-48 are product-by-process claims directed to an isolated, diverse population of peptides, polypeptides or proteins comprising stochastic amino acid sequences where the peptides are expressed from stochastically generated polynucleotide sequences, and

the stochastically generated polynucleotide sequences used to express the population of peptides are generated by copolymerization of oligonucleotides or chemical synthesis. Since both the processes of joining or ligating together oligonucleotides and chemically synthesizing oligonucleotides were well known in the art at the time the Kauffman application was filed, i.e., see Maniatis, (1982) pp. 11-14 (attached), claims 45-48 would have been apparent to those of ordinary skill in the art in view of the method already set forth in '323 claim 1, which recites a method of identifying a peptide, polypeptide or protein from a stochastic population of peptides or proteins expressed from a population of stochastic polynucleotide sequences. Thus, claims 45-48 are an apparent extension of '323 claim 1, and would correspond to the Count since '323 claim 1 is part of the Count, even though they also correspond to the Count because they are part of the Count.

Thus, all of the claims of the Kauffman '323 patent correspond to the proposed Count, because they are included as an alternative, are dependent on those included, or are obvious over those included as part of the Count.

The Kauffman '192 Patent

'192 claims 1-5

The proposed Count includes Kauffman '192 claim 1 joined by "or" to independent claims from the other five Kauffman patents. Kauffman '192 claim 1 thus corresponds exactly

to one part of the proposed Count. Because of the use of "or," correspondence to one part of the proposed Count is sufficient.

Kauffman '192 claims 2-5 are dependent on '192 claim 1 and therefore define the same patentable invention. '192 claims 2-5 therefore also correspond to the Count. In particular, claims 2 and 3 specify that the predetermined property of the peptide, polypeptide or protein produced by the method of '192 claim 1 has a "binding property" defined as an antigenic epitope, which may be identified by specific antibodies, respectively. Since screening by virtue of antibody reactivity was a well known technique at the time the Kauffman application was filed, i.e., see Matteucci and Heyneker (1983), describing a radioimmune assay (RIA) of transformed cells expressing recombinant protein, a peptide or protein having such a "binding property" would be an obvious extension of the method of '192 claim 1 given the state of the art at the time.[10]

Likewise, '192 claims 4 and 5 further specify that the proteins identified using the antibody are used to make a vaccine, and more specifically, an anti-hepatitis vaccine. Using peptides and proteins to vaccinate animals against subsequent infection by the native foreign agent were well known in the art at the time the Kauffman application was filed, i.e., see

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Applicants note that, although screening for proteins which bind to particular antibodies was known at the time that the invention was filed, it is Applicant's position that Pieczenik nevertheless presents a separately patentable species in that the random sequences are limited to a distinct number of amino acids, which requires particularity in the manner in which the random sequences are screened for antigenic epitopes. This point is discussed more in depth in Section V of this Request.

McAleer et al. (1984), which describes a hepatitis vaccine made from recombinantly produced viral protein; and Kleid et al. (1981), which describes the use of recombinantly produced foot-and-mouth disease viral protein as a vaccine (both attached). Therefore, claims 4 and 5 are obvious over the method recited in '192 claim 1 in view of the state of art at the time, and would therefore also correspond to the Count.

The Kauffman '483 Patent

The proposed Count includes Kauffman '483 claims 1-4, 6, 17, 29, 35, and 36 joined by "or" to independent claims from the other five Kauffman patents. Kauffman '483 claims 1-4, 6, 17, 29, 35, and 36 thus each correspond exactly to one part of the proposed Count. Because of the use of "or," correspondence to one part of the proposed Count is sufficient.

'483 claims 1 and 2

While '483 claim 1 exactly corresponds to one part of the Count, it would also correspond to the Count because it is obvious in view of '192 claim 1 when taken in view of the state of the art at the time the first Kauffman application was filed. '483 claim 1 is directed to a process for the production of a peptide, polypeptide or protein identified by screening or selecting host cells carrying a library of expression vectors containing stochastically generated polynucleotide sequences, whereby the polynucleotide sequences are generated by "synthetic polynucleotide coupling." While the meaning of the phrase "stochastic polynucleotide

coupling" is not clear in view of the '483 specification, it may refer to a method whereby stochastic sequences are produced by ligating stochastic oligonucleotides together to form a larger polymer. Since it was known in the art that oligonucleotides both with and without cohesive ends could be ligated together, i.e., see Maniatis, (1982) pp. 8-9, and Lewin, Genes II, John Wiley & Sons, N.Y. (1983), p. 285 (attached), building stochastic sequences in this manner would merely be an apparent variation of the main concept of generating stochastic sequences, to be screened for a predetermined property. Thus, while '483 claim 1 corresponds exactly to part of the Count, it also corresponds to the Count because it is an apparent variation of the method recited in claim 1 of Kauffman '192.

'483 claim 2 also corresponds exactly to part of the Count. Yet, '483 claim 2 would also correspond to the Count in view of, at the very least, '192 claim 1, since the only substantive difference between the claims is that '483 claim 2 specifies that the polynucleotides produced are "at least partially" stochastic. Since "completely" is a species of "at least partially," clearly one could generate "at least partially" stochastic sequences if one knew how to generate completely stochastic sequences. Indeed, one generates "partially" stochastic nucleotide sequences when cloning a population of completely stochastic nucleotide sequences into an expression vector. Thus, '483 claim 2 would be obvious over '192 claim 1 and '483 claim 1, and therefore corresponds to the Count as an apparent variation as well as an exact part of the Count.

'483 claims 3-5

'483 claims 3 and 4 are directed to methods of detecting a ligand by screening a population of peptides, polypeptides or proteins produced by stochastically generated polynucleotide sequences. Claim 3 merely differentiates over claim 4 by specifying that the stochastic polynucleotides are produced by synthetic coupling, which was a well known way to synthesize a polynucleotide sequence at the time the Kauffman application was filed as discussed above. Thus, '483 claims 3 and 4 are each merely an alternative way of looking at a method of screening a population of peptides for the ability to bind to a ligand. Thus, '483 claims 3 and 4 are apparent variations of, at the very least '192 claim 2, and would therefore correspond to the Count in an obvious manner, even though each exactly corresponds to part of the Count. In addition, since '483 claim 5 is dependent on either claim 3 or 4, it is directed to the same patentable invention and also corresponds to the Count.

'483 claims 6-16

'483 claim 6 exactly corresponds to part of the Count. '483 claims 7-16 either directly or indirectly depend from claim 6, and therefore define the same patentable invention. Thus, claims 7-16 also correspond to the Count. For instance, translating polynucleotide sequences to produce polypeptides (as recited in '483 claims 7 and 10) was certainly known in the art. Indeed, the basic premise of recombinant DNA technology was to express nucleic acid sequences, i.e., transcribe and translate, to produce recombinantly derived proteins.

Synthesizing "at least partially" stochastic sequences as recited in claims 8 and 11 would be an obvious extension of the synthesis of completely stochastic sequences as discussed above. Of course, it was also known that sequences could be cloned and "amplified" in vivo (as encompassed by '483 claim 9) by virtue of high copy number cloning vectors at the time the first Kauffman application was filed, i.e., see Muller et al. (1978), p. 345 (attached). Likewise, isolating a cloned polynucleotide sequence by isolating a plasmid was also known, i.e, see id.(attached). Again, screening by binding or chemical catalysis, as recited in '483 claims 13, 15 and 16, was a well known way to screen a library at the time, as was improving a predetermined property by mutagenesis as recited in '483 claim 14 (see the instant specification at page 8, lines 4-5, discussing McClure (1985) Ann. Rev. Biochem. 54: 171-204).

'483 claims 17-28

'483 claim 17 corresponds exactly to part of the Count. Claims 18-28 are dependent on claim 17 in much the same manner as claims 7-16 are dependent on claim 6, which was discussed at length above. Thus, claims 18-28 also correspond to the Count in that they define the same patentable invention as '483 claim 17.

For instance, claim 24 is dependent on claim 17 and specifies that step (d) of claim 17, "producing said peptide or protein," comprises "chemical synthesis or recombinant expression." Thus, claim 24 merely states that the protein may be produced recombinantly using the

polynucleotide identified in step (c), or may be synthesized chemically, presumedly based on knowledge gleaned from the nucleotide sequence of the isolated polynucleotide. However, the use of genetic information to express proteins, and chemical synthesis of peptides based on genetic information, were both known in the art the time the Kauffman application was filed. See, i.e., "The Science Used in the Recombinant DNA Industry," Chapter 18 from Watson, Tooze and Kurtz (1983) (attached). Thus, it would have been clear to those of skill in the art when faced with claim 17 of the '483 patent that the peptide, polypeptide or protein could be produced recombinantly or synthetically. Claim 24 therefore corresponds to the Count, because it is directed to the same patentable invention as claim 17 of the '483 patent.

'483 claims 29-34

'483 claim 29 corresponds exactly to part of the Count. Claims 30-34 are dependent on claim 29 and merely specify various known ways to synthesize polynucleotide sequences. Thus, claims 30-34 define the same patentable invention as '483 claim 29, and are obvious in view of claim 29 and the state of the art at the time the Kauffman application was filed. Thus, '483 claims 30-34 also correspond to the Count.

'483 claims 35-38

'483 claims 35 and 36 correspond exactly to individual parts of the Count. In addition, it is noted that claims 35 and 36 merely recite in alternative ways known uses of a peptide or

protein to catalyze a reaction between two or more reactant precursors. Given that the method of the invention permits the identification or isolation of specific peptide or protein sequences from a stochastic population by any means, including by virtue of their capability to catalyze a chemical reaction, claims 35 and 36 merely recite what would have been a standard use of a stochastic population of peptides or proteins given the state of the art. Thus, '483 claims 35 and 36 correspond to the Count not only because they are individually included in the Count, but also because they would have been obvious over the other claims, i.e., '483 claims 6 or 17 at the least.

Claims 37 and 38 are dependent on claim 36 of the '483 patent and merely specify that the steps are repeated on a smaller population taken from the entire population of stochastic peptides, polypeptides or proteins. Thus, claims 37 and 38 define the same patentable invention, and also correspond to the Count.

'483 claims 39-53

Claims 39-53 are dependent on either claim 6, claim 17 or claim 29, each of which corresponds exactly to part of the Count. In fact, claims 39-53 merely specify various sizes of populations of amino acid and polynucleotide sequences which may be employed in the methods recited in the independent claims. Since size of the stochastic library would not constitute a patentable distinction over the general method, claims 39-53 also correspond to the Count.

Thus, all of the claims in the Kauffman '483 patent correspond to the proposed Count.

The Kauffman '514 Patent

The proposed Count includes Kauffman '514 claims 1, 11, 12, 18, 27 and 37 joined by "or" to independent claims from the other five Kauffman patents. Kauffman '514 claims 1, 11, 12, 18, 27 and 37 thus each correspond exactly to one part of the proposed Count. Because of the use of "or," correspondence to one part of the proposed Count is sufficient.

'514 claims 1-10

'514 claims 2-10 are dependent on '514 claim 1. Thus, claims 2-10 define the same patentable invention as claim 1, and would also correspond to the Count. For instance, claims 3 and 7 add that the process for producing an expression vector comprising a stochastic sequence of polynucleotides as recited in '514 claim 1 includes a further step whereby the vector is cut with a restriction enzyme and religated. As discussed above, generating new sequences by ligating together restriction fragments was known at the time the Kauffman application was filed. See, i.e., Shortle (1983). Thus, claims 3 and 7 do not patentably distinguish over '514 claim 1.

'514 claims 11-12

'514 claim 11 corresponds exactly to part of the Count. Nevertheless, claim 11 would

also be obvious in view of various other claims which also correspond exactly to the Count in that it merely recites a method which involves a specific way of synthesizing stochastic polynucleotide sequences. Specifically, the method requires addition of polynucleotides to the 3' end of a linearized vector with terminal transferase in order to synthesize a stochastic sequence, and a filling in of the second strand with a polymerase enzyme, both of which were known in the art at the time the Kauffman application was filed, and would have been apparent ways to synthesize a stochastic population of polynuclectides given the concept and motivation to do so. See, i.e., Damiani et al. (1982) (attached).

'514 claim 12 corresponds exactly to part of the Count. '514 claims 13-17 are dependent on claim 12, and some are alternatively dependent on claim 1 or 11. Yet none of claims 13-17 provides a patentable distinction over the independent claims on which they depend. In fact, claims 13, 14 and 17 are product-by-process claims, and claim 15 merely specifies that the translation product is selected from the group consisting of a peptide, polypeptide or a protein. Claim 16 indicates that the transcription product can be RNA or DNA. Given the fact that reverse transcription of RNA to generate a cDNA was known in the art at the time the Kauffman application was filed, i.e., see Rhode et al. (1981), it would have been clear to one of skill in the art that the claimed method could be applied just as easily to a stochastic population of RNA as well as DNA. Thus, claims 13-17 do not patentably distinguish over the claims on which they depend. Since the Kauffman independent claims all correspond exactly to part of the Count, '514 claims 13-17 also correspond to the Count.

'514 claims 18-26

'514 claim 18 also corresponds exactly to part of the Count. Even so, it is noted that claim 18 is similar to claim 12 in that it is directed to a method of producing a library or population of vectors, but claim 18 specifies that the size of the library is greater than about 1 X 10^5, and that the library may be synthesized by stochastic polymerization of double stranded oligonucleotides or nucleotide triphosphates presumedly directly on the vector, whereas claim 12 specifies that the stochastic sequences are first synthesized, then ligated into the vector. Since neither the size of the library nor the manner of synthesizing the stochastic sequences provides a patentable distinction over the general concept and motivation for doing so, claim 18 would also correspond to the Count because it is an apparent variation of claim 12. Likewise, since claims 19-26 are dependent on claim 18, they would also correspond to the Count since they define the same patentable invention as '514 claim 18, in much the same manner as several other sets of Kauffman dependent claims discussed at length above.

'514 claims 27-36

'514 claim 27 also corresponds exactly to part of the Count. However, claim 27 is also obvious over either claim 12 or claim 18 of the '514 patent since it recites a method of copolymerizing vectors containing double-stranded polynucleotides, and vectors are actually a form of polynucleotides. Hence, claim 27 corresponds to the Count also because it is obvious over claims 12 and 18 of the '514 patent. Furthermore, since claims 28-36 are dependent on

claim 27 and therefore define the same patentable invention, '514 claims 28-36 also correspond to the Count.

'514 claims 37-46

'514 claim 37 corresponds exactly to part of the Count. However, '514 claim 37 is merely an extension of claim 18 in that it recites a method of stochastically copolymerizing double-stranded polynucleotides onto vectors which already contain stochastic or diverse polynucleotide sequences. Adding further stochastic sequences to vectors which already contain such sequences to begin with is really no different than a method of adding stochastic sequences to a vector as recited in claim 18. Thus, '514 claim 37 also corresponds to the Count in that it would have been obvious in view of claim 18. Claims 38-46 of the '514 patent are dependent on claim 37, and would therefore correspond to the Count because they define the same patentable invention as '514 claim 37.

Thus, all the claims in the Kauffman '514 patent correspond to the proposed Count.

The Kauffman '476 Patent

The proposed Count includes Kauffman '476 claims 1-3, 8, 14, 15, 29, 47, 61, 79, 91 and 103 joined by "or" to independent claims from the other five Kauffman patents. Kauffman '476 claims 1-3, 8, 14, 15, 29, 47, 61, 79, 91 and 103 thus each correspond exactly to one

part of the proposed Count. Because of the use of "or," correspondence to one part of the proposed Count is sufficient.

'476 claims 1, 2 and 8

Although '476 claim 1 corresponds exactly to part of the Count, '476 claim 1 would also correspond to the Count in view of '514 claim 12, since the only substantive difference between these claims is that '476 claim 1 adds a step of using the isolated vector or polynucleotide sequence to produce a transcription or translation product having the predetermined property. The fact that nucleic acids could be used to transcribe or translate desired products was well known in the art at the time the Kauffman application was filed. Thus, '476 claim 1 would have been an apparent extension of '514 claim 12, therefore '476 claim 1 would correspond to the Count in this manner as well.

Likewise, '476 claim 2 corresponds exactly to part of the Count. However, '476 claim 2 is almost a precise duplicate of '476 claim 1, and would also correspond to the Count in an obvious manner in view of '514 claim 12. The only difference between '476 claims 1 and 2 is that claim 2 specifies that a "population" of stochastic polynucleotides is produced and inserted into a vector (rather than a single stochastic polynucleotide sequence as recited in '476 claim 1). Although the meaning of "stochastic" is not exactly clear in view of the '476 specification, it appears to have no meaning in the context of a single polynucleotide sequence, since some amount of diversity is apparently required. See, i.e., Kauffman '323, claim 24. If one isolates

a "stochastic" polynucleotide sequence, by implication, one isolates a stochastic population. Therefore, '476 claim 2 is obvious over '476 claim 1 and '514 claim 12, and would correspond to the Count in this manner as well.

Similarly, '476 claim 8 corresponds exactly to part of the Count. However, '476 claim 8 is obvious in view of '476 claim 1, since a method of producing an RNA is merely a subset of a method of producing a transcription product as claimed (as discussed above for '514 claim 16). Hence, '476 claim 8 also corresponds to the Count because it is obvious in view of '476 claim 1. Since '476 claims 9-14 are dependent on either claim 1, 2 or 8, these claims would also correspond to the Count since they define the same patentable invention.

'476 claims 3-7

'476 claim 3 corresponds exactly to part of the Count. Because '476 claims 4-7 are dependent on claim 3, they would also correspond to the Count because they define the same patentable invention. In particular, claims 4-7 specify that the polynucleotide produced by the method of claim 3 has a capacity to bind to a compound, which is more specifically defined as a protein, and even more specifically defined as a protein which controls the transcription or replication of DNA. It was known in the art at the time the Kauffman application was filed that some genes contain an "enhancer" region which regulates transcription from the promoter. For instance, see the attached abstracts of Weiner and Botchan (1984); Zaret and Yamamoto (1984); Jost et al. (1984); and Pavvar et al. (1983), each of which describes proteins which

bind to upstream enhancer elements. Similarly, see the chapter entitled "The Genetic Elements That Control Gene Expression" from Watson, Tooze and Kurtz (1983), where the action of inducers and repressors of gene expression is illustrated by reference to the lactose operon of E. coli. Thus, dependent claims 4-7 are obvious in view of independent claim 3 when viewed against the state of the art at the time, and would also correspond to the Count.

'476 claims 15-28

Likewise, '476 claim 15 corresponds exactly to part of the Count. Because '476 claims 16-28 are dependent on claim 15, they would also correspond to the Count since they define the same patentable invention. For instance, claim 17 further specifies that the population of stochastic polynucleotide sequences is amplified. It was common knowledge in the art at the time the Kauffman application was filed that cloned DNA could be amplified in vivo using certain plasmid vectors. See, i.e., Muller et al. (1978), p. 345, which describes chloramphenicol-induced amplification of cloned DNA in a plasmid, and Maniatis, (1982) p.3.

Claims 19 and 20 are also dependent on claim 15 and specify that the claimed polynucleotides can be either RNA or DNA. It was known in the art at the time the Kauffman application was filed that RNA's could have "predetermined properties" other than the translation of proteins. For instance, see Pace and Marsh (1985) which reviews types of catalytic RNA known at the time, and Guerrier-Takada et al. (1983), which describes the

catalytic activity of the RNA moiety of E. coli ribonuclease P in cleaving tRNA precursors. See also, Rhode et al. (1981), disclosing the synthesis of cDNA from RNA using reverse transcriptase. Thus, it would have been apparent to those of ordinary skill in the art when presented with '476 claim 15 that "polynucleotide" could also refer to RNA in a variety of contexts, given the many biological functions of RNA. Thus, claims 19 and 20 would correspond to the Count because they provide no patentable distinction over claim 15, on which they are dependent, and claim 15 exactly corresponds to part of the Count.

Also, claim 23, as another example, is indirectly dependent on claim 15 and specifies that the claimed method further comprises improving the predetermined property of the polynucleotide by in vitro or in vivo mutagenesis. This also would have been a well known extension of the method recited in claim 15, as discussed previously and reviewed in the present specification at page 35, lines 2-3 and page 8, lines 4-5.

'476 claims 47-60

Although claim 47 of the '476 patent corresponds exactly to part of the Count, it is noted that claim 47 would also correspond to the Count because it is obvious over '476 claim 15. The only distinction between these two claims is that '476 claim 47 adds a step of isolating the polynucleotide sequence identified as having a predetermined property. Since methods of isolating polynucleotides were well known in the art at the time the Kauffman application was filed, claim 47 of the '476 patent would have been a clear extension of claim 15. Additionally,

since claims 48-60 are dependent on claim 47 in the same manner that claims 16-28 are dependent on claim 15, they would also correspond to the Count since they define the same patentable invention.

'476 claims 29-46

Similarly, claim 29 corresponds exactly to part of the Count. However, '476 claim 29 is also obvious in view of claim 15, since the only distinction is that it specifies that the predetermined property of the polynucleotide is the ability to bind a ligand. Proteins that bind to polynucleotide sequences were well known in the art at the time the Kauffman application was filed as discussed above, i.e., see Pavvar et al., which shows that transcriptional regulatory proteins which bind to DNA were known at the latest in 1983. Furthermore, the strategy of screening a DNA library by virtue of a binding activity was also known as discussed above and evidenced by Matteucci and Heyneker (1983). Thus, claim 29 would also be obvious in view of claim 15, and also corresponds to the Count in this manner.

Additionally, because claims 30-46 are dependent on '476 claim 29, they would also correspond to the Count because they define the same patentable invention. In particular, '476 claim 41 adds a further step whereby the population of vectors is digested with a restriction enzyme such that the cloned stochastic sequences are digested, then reinserted to create new sequences. Such techniques for reassembling or creating new DNA sequences were known in the art at the time the Kauffman application was filed as discussed above, i.e., see Shortle

(1983). Thus, the additional step recited in claim 41 would have been an obvious extension of the method recited in claim 29, and claim 41 would also correspond to the Count as being obvious in view of the state of the art.

'476 claims 61-78

'476 claim 61 is obvious in view of claim 29 in the same manner that claim 47 is obvious over 15. The only distinction between these two claims is that '476 claim 61 adds a step of isolating the polynucleotide sequence identified as having a predetermined property. Since methods of isolating polynucleotides were well known in the art at the time the Kauffman application was filed, claim 61 of the '476 patent would have been an obvious extension of claim 29. Additionally, since claims 62-78 are dependent on claim 61, they would also correspond to the Count since they define the same patentable invention. In particular, claim 73 adds a restriction/ re-ligation step as discussed above for claim 41, and would be obvious over claims 61 and 29 in view of the state of the art at the time, i.e., see Shortle (1983).

'476 claims 79-90 and 103-107

'476 claim 79 corresponds exactly to part of the Count. Nevertheless, it would also correspond to the Count in that it is obvious over any one of a number of claims in all five of the Kauffman patents. For instance, virtually all of the claimed methods require synthesis of a stochastic population of polynucleotide sequences that are the screened or selected by virtue of

a predetermined property. The only limitations added by claim 79 of the '476 patent are that the population has greater than 1 X 10^6 different sequences, and the sequences are synthesized by "stochastically copolymerizing" polynucleotides. In fact, claim 29 of the Kauffman '483 patent is broadly directed to a method of producing a stochastic polynucleotide population by any means, of any size. Thus, claim 79 of the '476 patent is a species of claim 29 of the '483 patent.

Moreover, the limitations of '476 claim 79 do not add a patentable distinction in view of the state of the art at the time the Kauffman patent was filed. For instance, it would have been self-evident that the random generation of polynucleotides will naturally result in very large numbers of polynucleotides, because the number of permutations increases exponentially for each randomly incorporated unit. For example, a polynucleotide comprising only ten randomly incorporated bases has 4^{10} or over 10^6 random permutations. Thus, the size of the population recited in claim 79 is not a patentable distinction.

Furthermore, it was certainly known that new sequences could be made by ligating smaller polynucleotides together, i.e., see Lewin (1983), p. 285, and Shortle (1983), teaching that restriction fragments with cohesive, partly complementary "sticky" ends can be ligated together to form new DNA sequences. Thus, assuming that "stochastic copolymerization" has such a meaning, this would have been merely one known way to synthesize a population of stochastic sequences given the general teaching of and motivation for the method as taught by the invention as a whole. Thus, the manner of synthesizing stochastic sequences does not

provide a patentable distinction.

Thus, '476 claim 79 would correspond to the count as obvious over the other claims, particularly claim 29 of the '483 patent, in view of the state of the art. Because claims 80-90 depend from claim 79, they define the same patentable invention and therefore would also correspond to the Count. In fact, claims 83 and 84 even specify that "stochastic copolymerization" is effected by hybridization of complementary sequences or by ligation, respectively, as already discussed above in reference to Maniatis (1982) and Shortle (1983).

Likewise, claim 103 corresponds exactly to part of the Count, but would also correspond in an obvious manner over claim 79. Claim 103 is directed to an isolated population of polynucleotides having greater than about 1 X 10^5 different sequences. If claim 79, a method of making a stochastic population of polynucleotide sequences, corresponds to the Count, then it follows that a population of stochastic polynucleotide sequences made thereby would also correspond. Thus, '476 claim 103 would also correspond to the Count because it is obvious over the other claims, as would claims 104-107 which depend from claim 103 and define the same patentable invention.

'476 claims 91-102

Finally, claim 91 of the '476 patent corresponds exactly to part of the Count. Even so, claim 91 would also be obvious over any one of a number of Kauffman claims in any of the five patents discussed herein, and would correspond to the Count in this manner as well. For

instance, claim 91 recites a method of producing a diverse population of polynucleotides by stochastically copolymerizing polynucleotides which have been "cleaved," presumedly by a restriction endonuclease. Yet such a manner of producing nucleotide sequences was known in the art at the time as evidenced by Shortle (1983) and discussed above. Thus, claim 91 of the '476 patent does not provide a patentable distinction over any claim which recites a method of producing stochastic polynucleotide sequences, given the state of the art at the time. Since virtually all the method claims of the five Kauffman patents require a step whereby a population of stochastic sequences is synthesized, a claim merely reciting a particular, but known, method of doing so would not patentably distinguish over the general method.

Thus, claim 91 of the '476 patent also corresponds to the Count in that it is obvious over the other claims. Because claims 92-102 depend from claim 91 and define the same patentable invention, claims 92-100 would also correspond to the Count in much the same manner as the other sets of dependent claims discussed at length above.

Thus, all the Kauffman '476 claims correspond to the proposed Count.

The Kauffman '862 Patent

The proposed Count includes Kauffman '862 claims 1-3, 9, 17 and 26 joined by "or" to independent claims from the other five Kauffman patents. Kauffman '862 independent claims 1-3, 9, 17 and 26 thus each correspond exactly to one part of the proposed Count. Because of

the use of "or," correspondence to one part of the proposed Count is sufficient.

'862 claim 1

Although '862 claim 1 corresponds exactly to part of the Count, '862 claim 1 would also correspond to the Count in view of Kauffman '514 claim 1, for instance, because the method of '862 claim 1 is the same as '514 claim 1 except that it includes a step whereby one vector comprising a stochastic sequence is transformed into a competent host cell. Transformation techniques were well known in the art at the time that the '862 invention was made, therefore, the additional step transformation step in order to generate a transformed host cell is not a patentable distinction over '514 claim 1.

'862 claim 1 also specifies that the transformed host cell is capable of producing a transcription or translation product by virtue of the expression vector it comprises. The fact that nucleic acids could be used to transcribe or translate desired products was also well known in the art at the time the Kauffman application was filed. Thus, '862 claim 1 would have been an apparent extension of '514 claim 1, therefore '862 claim 1 would correspond to the Count in this manner as well.

'862 claim 2

Although '862 claim 1 corresponds exactly to part of the Count, '862 claim 2 would also correspond to the Count in view of '862 claim 1, because the method of '862 claim 2 has

the same goal as '862 claim 1 except that it using another means which was known in the art at the time. Specifically, whereas the method of '862 claim 1 polymerizes oligonucleotides to form stochastic sequences, the method of claim 2 uses terminal transferase in the presence of deoxynucleotide triphosphates. Ligation of oligonucleotides and terminal transferase were both known in the art at the time as ways to generate longer nucleotide sequences as evidenced by Shortle and Damiani as discussed above. Therefore, the fact that the method of '862 claim 2 uses a different means of generating stochastic sequences than '862 claim 1 does not provide a patentable distinction. Thus, '862 claim 2 would also correspond to the Count in this manner as well.

'862 claims 3-8

Although '862 claim 3 corresponds exactly to part of the Count, '862 claim 3 would also correspond to the Count in view of '862 claims 1 and 2 taken with '483 claim 1, for instance. Indeed, the method of '862 claim 3 only differs from claims 1 and 2 of that patent in that it includes the additional steps whereby the claimed transformed host cell is isolated by a screening or selection step. Since such a step is also encompassed within '483 claim 1 and a variety of other claims included in the Count, '862 claim 3 would also correspond to the Count in this manner.

'862 claims 4-8 are dependent on claims 1-3, and do not provided any patentable distinction over the base claims in view of the state of the art at the time. In fact, claim 4

merely claims the host cell isolated by the methods of claims 1-3, and claim 5 merely rephrases the method by specifying that the transformed stochastic sequence is a template for the synthesis of a transcription or translation product, which is rather redundant in view of the preamble of claims 1-3. Claims 6 and 7 more particularly define the translation and transcription products, respectively, by specifying that the translation product may be peptide, polypeptide or protein, and the transcription product may be DNA or RNA. These are generic categories of products which provide no patentable distinction over the general terms "transcription product" and "translation product" given the state of the art at the time. Finally, claim 8 merely specifies that the size of the library of expression vectors comprises stochastic sequences coding for at least 10,000 peptides, polypeptides or proteins. The size of the library provides no patentable distinction as discussed above, because it would have been self-evident that the random generation of polynucleotides will naturally result in very large numbers of polynucleotides, because the number of permutations increases exponentially for each randomly incorporated unit. For example, a polynucleotide comprising only ten randomly incorporated bases has 4^{10} or over 10^6 random permutations.

'862 claims 9-16

Although '862 claim 9 corresponds exactly to part of the Count, '862 claim 9 would also correspond to the Count in view of '862 claims 1-8 as a whole. For instance, like claims 1 and 2 of the '862 patent, claim 9 provides a variety of alternatives for producing stochastic

sequences which are then used to produce a library of expression vectors. However, claim 9 recites a method of producing a diverse population of host cells rather than just a single host cell comprising a vector containing a stochastically-generated sequence. Because transformation protocols in general deal with a large quantity of DNA and a large population of competent cells, claiming a transformed cell in the singular or the plural is merely a matter of semantics, and does not provide any distinction in the methods employed (other than perhaps a screening or selection step to isolate a particular transformed cell).

Claims 10-16 are dependent on claim 9, and do not provide any patentable distinction given the state of the art at the time. For instance, claims 10 and 11 merely increase the size of the library of stochastic sequences. As discussed above, the fact that the size of the library will increase with the length of the random sequences is self-evident, and does not provide a patentable distinction in the absence of unexpected results, difficulties or advantages (none of which is disclosed in Kauffman '862). The fact that claim 15 claims "at least partially stochastic" sequences is not distinctive as discussed above because, if one can generate fully stochastic sequences, one can also generate partially stochastic sequences and indeed does so when cloning a fully stochastic sequence into a cloning vector. Claim 16 provides a further step whereby the ligated vectors are digested with a restriction enzyme that only cuts within the stochastic insert portion, and the vectors are re-ligated to generate new sequences. Such techniques for reassembling or creating new DNA sequences were known in the art at the time the Kauffman application was filed as discussed above, i.e., see Shortle (1983). Thus, none of

the dependent claims 10-16 provide a patentable distinction over claim 9, and would therefore be covered by the proposed Count to the extent that claim 9 is covered given the state of the art at the time.

'862 claims 17-25

Although '862 claim 17 corresponds exactly to part of the Count, '862 claim 17 would also correspond to the Count because it merely re-phrases in broader terms the method recited in '862 claim 9. In like manner, claims 18-24 merely repeat the limitations of claims 10-14 with regard to the size of the library and the manner in which stochastic sequences may be generated. And claim 25 is merely an extended abstraction by reciting that the claimed diverse population of vectors comprises two or more diverse populations of vectors. How many diverse populations are contained within a single diverse population merely depends on how many ways one can envision separating the members of a population according to different characteristics.

'862 claims 26-34

Finally, although '862 claim 26 corresponds exactly to part of the Count, it would also correspond to the Count due to the fact that it also merely re-phrases in broader terms the method recited in '862 claim 9 (which in turn corresponds to the Count for the reasons provided above), and also includes the concept recited in claim 16 discussed above whereby

vectors with stochastic sequences are digested with restriction enzymes and ligated back together. As this concept does not provide a patentable distinction over other methods of generating stochastic sequences given the state of the art at the time, i.e., Shortle (1983), claim 26 would also correspond to the Count by virtue of its similarity to the claims discussed above. Claims 27-34 again repeat the limitations of claims 18-25 except that they are dependent on claim 26 rather than claim 17. Nevertheless, they fail to provide a patentable distinction over independent claim 26 for the same reasons discussed above, and would therefore also correspond to the Count.

Thus, all the claims in the Kauffman '862 patent correspond to the proposed Count.

IV. CLAIMS OF THE HORWITZ APPLICATION WHICH CORRESPOND TO THE PROPOSED COUNT PURSUANT TO 37 CFR §1.607(a)(4)

As discussed in the original Request for Interference filed on June 9, 1999, claims 15-25 of the instant application are believed to correspond to the proposed Count. In addition, claims 3, 4, 6-8 and 11-14 submitted March 3, 1999, also correspond to the Count. The proposed Count includes all these claims joined by "or" to each other and to each of the Kauffman independent claims as discussed above. Each of the instant pending claims thus corresponds exactly to one part of the proposed Count. Because of the use of "or," correspondence to one part of the proposed Count is sufficient. Appendix B of the original

Request contained a chart providing an element-by-element recitation of claims 3, 4, 6-8, 11-25 of the instant application and exemplary support in both the originally filed and present application. [11] That Appendix is not repeated here, because the amendments to the claims included herein introduced no new matter and were merely made to clarify the claim language. Thus, the original showing of support should still be sufficient.

By way of amendment, new claims 26 and 27 have been added above. These claims also correspond to the Count and were drafted based on claims 1 and 2 of the Kauffman '862 patent using the language of the instant specification. The proposed Count includes these claims joined by "or" to each other and to each of the other claims in the instant application and to each of the Kauffman independent claims as discussed above. Each of the instant pending claims thus corresponds exactly to one part of the proposed Count.[12] Because of the use of "or," correspondence to one part of the proposed Count is sufficient. Appendix C of this Renewed Request for Interference contains a chart providing an element-by-element recitation of claims 26 and 27, and shows where support may be found in the instant application as well

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[11] The present Horwitz application is the latest in a chain of continuation applications which begin with Serial No. 06/887,070, filed July 17, 1986. The present application is a continuation-in-part relative to the first application.

Again, applicants note that there are two proposed Counts in Appendices A and B, respectively. The Count proposed in Appendix A includes the independent claims of all six Kauffman patents, the claims of the instant application and the independent claims of Pieczenik in the alternative. The claim proposed in Appendix B is an alternative Count which does not include the Pieczenik claims, given that Applicants do not believe that Pieczenick should be included in the interference.

as in the parent application 06/887,070.

V. THE CLAIMS OF THE PIECZENIK '363 PATENT SHOULD NOT BE INCLUDED IN THE REQUESTED INTERFERENCE

It is the Examiner's opinion that the claims of Pieczenik '363 correspond to and define the same patentable invention as the claims of the instant Horwitz application, as discussed in the Examiner interview on August 18, 1999 and reiterated in the Office Action dated October 14, 1999. In contrast to what the Examiner believes, Applicants believe that Pieczenik should not be included in the interference because it claims a patentably distinct species within the broader genus claimed in the instant application and the Kauffman patents. This species is evidenced by the particular vector and screening system required by the Pieczenik claims, a system which was not disclosed, incidentally, until the CIP application was filed on February 28, 1991.

All the claims of the instant Horwitz application and the Kauffman patents are essentially directed to or based on generic methods of searching for biologically active nucleotide sequences from among a randomly or stochastically generated population, on the theory that particular novel sequences capable of predetermined or desired biological functions may be identified. The crux of the invention reflected in the Kauffman and Horwitz claims rests on the discovery, which was indeed a "leap of faith" at the time the present invention was made, that randomly generated sequences could perform specific biological functions in the

absence of millions of years of evolutionary refinement.

At the outset, applicants note that the crux of the Pieczenik invention is different. Pieczenik discloses a method of epitope mapping whereby antigenic epitopes on known proteins, or the antigenic specificity of known antibodies, is established using a library of short (4-12 amino acid) peptides. Antibody binding is very specific. In fact, when one identifies a peptide specific for a given antibody where the antibody was generated by immunizing with a specific protein, one is not identifying a novel sequence which, by a leap of faith happens to have the same function as the original protein. Rather, one is identifying a particular sequence in the original known protein by virtue of the characteristic of antibody binding. Indeed, this goal is reflected throughout the Pieczenik disclosure. For instance, Example I of Pieczenik discloses the identification of specific antibody recognition sites on insulin by immunizing with insulin and then using a peptide library to determine to what protein sequences the antibodies generated bind. There is no identification of novel sequences; the method merely characterizes a protein interaction which already exists.

This concept is further emphasized by the evaluating the utility of the Pieczenik methods. For instance, in the Pieczenik Reply dated November 22, 1989, the applicants state that "of course, one need not screen random peptides against random antibodies. One can also either screen random peptides against specific antibodies, or random antibodies against specific peptides." However, it would seem that one must do one of the latter in order to identify a peptide or an antibody having any sort of utility. How would you ever recognize the

significance of any particular peptide or any particular antibody if you merely screened random against random? So you might identify a random antibody that binds to a random peptide. What utility does this antibody have if you have no reference for the peptide, i.e., what utility is there in knowing that a random antibody binds to a particular short peptide without knowing what proteins that peptide is a part of, and in which proteins that peptide takes on an active conformation such that the antibody can be utilized?

Furthermore, even if a utility could be established for screening random antibodies with random peptide libraries, such a method was not enabled by Pieczenik using the short peptides disclosed until the CIP application was filed on February 28, 1991. It is one thing to screen antibodies isolated from an *immunized* animal using a peptide library. Here, as with Example I in Pieczenik, a higher than random proportion of the antibodies will recognize the protein used for immunization, and if the random peptide library is generated directly from sheared cDNA encoding the protein used for immunization (as it was in Pieczenik's Example I), there may be a chance of identifying a specific antibody using such a library in a lytic phage vector, i.e., λgt11, as used in Example I of Pieczenik. In this instance, however, the library is not truly random because it is generated using sheared cDNA encoding the actual protein.

A lytic phage vector system such as λgt11 would never work if one were trying to screen a truly random population of short peptides. For one, the phage would lyse the cells and all cellular proteins would be exposed and perhaps even degraded into shorter peptides. How would one ever distinguish whether a given antibody is binding to the cloned random

peptide, or to some other peptide from the lysed cell? Moreover, with no pre-immunization of an animal with a protein of interest, one would theoretically be screening every antibody which could conceivably be generated by clonal selection. Such a population of antibodies would include antibodies that recognize cellular peptides in addition to the random peptides cloned into and expressed by the phage vectors. It would be virtually impossible to identify a binding interaction between a random antibody and a random peptide using such a system.

Thus, Pieczenik did not enable his epitope library until he disclosed the filamentous f1 phage vector system in the CIP application filed on February 28, 1991 (see Example IV of the Pieczenik '363 patent). In fact, at the time the parent Pieczenick application was filed, the special issues of improper folding and degradation were inherent in working with small peptides, and these problems were not overcome until the phage display technology developed. This phage does not lyse the host cells as it multiplies, but buds through the surface of the cell to generate new phage particles. By cloning nucleotide sequences encoding peptides into the coat protein gene of the phage, the peptides are displayed on the cell surface and become part of the phage coat as the phage multiplies. Thus, random peptides expressed in this manner can be screened without the excess "noise" generated by release of cellular proteins.[13]

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[13] Note that the "noise" generated from cellular proteins could also be avoided by immobilizing random peptides as suggested in Pieczenik Example V, also added when the CIP was filed on February 28, 1991. However, Pieczenik employed neither a random library of peptides nor a random library of antibodies. In fact, antibodies specific for the N-terminus of endoplasmin were prepared, purified and then allowed to bind to immobilized peptides generated directly from the N-terminal sequence of endoplasmin.

In fact, George Pieczenik himself admits that he did not have evidence of the "operability of the invention" until he performed experiments with the filamentous phage system, as described in the Declaration of Pieczenik submitted with the Reply dated May 15, 1992 (Declaration was pursuant to 37 CFR 1.131; see p. 7, second full paragraph, attached as Exhibit I). There is significant evidence that he had not performed these experiments until after the grandparent application was filed.

For instance, the Pieczenik Declaration was submitted along with others in order to antedate a prior art reference dated August, 1990, whereas no antedating Declarations were submitted in rebuttal to the Ballivet (Kauffman) reference, dated 1987. Furthermore, as described in his Declaration, Pieczenik used the data gathered from these experiments to seek the support of "potential corporate research sponsors" admittedly some time "after the filing of USSN 770,390, filed August 25, 1985" (see Exhibit I, page 2).

Moreover, he sent a draft manuscript describing these experiments to his attorney, Lorance Greenlee, along with a letter describing the manuscript as "fairly hot off the presses" (see Exhibit J, containing a Declaration by Lorance Greenlee also attached to the May 15th Response, and the letter from Pieczenik attached thereto). Because Lorance Greenlee only began representing Pieczenik in June of 1987, the draft manuscript could not have been "hot off the presses" any earlier than this date (see Exhibit J, paragraph 2).

Thus, the evidence suggests that Pieczenik did not believe, nor did he have evidence, that his invention would work at the time the grandparent application was filed. Moreover, the

disclosure which describes the enabling information was not added until the CIP application was filed on February 28, 1991.[14]

Therefore, while the present invention and that of Kauffman is directed to screening random nucleic acids and peptides in general for a variety of desired biological functions, Pieczenik particularly concerns the screening of short random peptide populations (4 to 12 amino acids) specifically for antigenic epitopes using a particular expression system, a filamentous phage vector that was not enabled until the Pieczenik CIP application was filed on February 28, 1991. Applicants therefore conclude that Pieczenik is directed to a specific application of the broader concept requiring specific vector systems for specific screening purposes, and therefore at the most constitutes a separately patentable species within a prior patentable genus. Accordingly, Pieczenik should not be included in the interference.

VI. EXPLANATION OF HOW THE REQUIREMENT OF 35 U.S.C. §135(b) IS MET

According to 35 U.S.C. §135(b), "[a] claim which is the same as, or for the same or substantially the same subject matter as, a claim of an issued patent may not be made in any application unless such a claim is made prior to one year from the date on which the patent was granted." In the instant case, the Kauffman '323 Patent issued on March 3, 1998. Claims 3, 4, 6-8 and 11-14 of the instant application were filed in a preliminary amendment in the instant

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[14] Indeed, Pieczenik did not refer to his oligonucleotides as "random" until the CIP was filed (see Exhibit G attached to the Reply to Examiner interview filed September 24, 1999, material added to pages 6-7).

application on March 3, 1999. These claims are for "the same as, or for the same or substantially the same subject matter as" claims 1, 16, 24, 25, 34 and 41 of the Kauffman '323 patent, and were present prior to one year from the date on which the Kauffman '323 Patent issued.

Likewise, the Kauffman '192 Patent issued on June 9, 1998. Claim 15 of the instant application was submitted in the Supplemental Preliminary Amendment filed on June 9, 1999. Claim 15 is for "the same as, or for the same or substantially the same subject matter as" the claim 1 of the Kauffman '192 patent, and was present prior to one year from the date on which this patent issued.

The Kauffman '483 patent issued on October 6, 1998. Claims 16-20 of the instant application were submitted in the Supplemental Preliminary Amendment filed on June 9, 1999. Claims 16-20 are for "the same as, or for the same or substantially the same subject matter as" claims 6, 17, 29, 35 and 36, respectively, of the Kauffman '483 patent, and were present prior to one year from the date on which this patent issued.

The Kauffman '514 patent issued on October 20, 1998. Claims 21-23 of the instant application were submitted in the Supplemental Preliminary Amendment filed on June 9, 1999. Claims 21-23 are for "the same as, or for the same or substantially the same subject matter as" claims 1, 12 and 18, respectively, of the Kauffman '514 patent, and were present prior to one year from the date on which this patent issued.

The Kauffman '479 patent issued on September 29, 1998. Claim 24 was submitted in

the Supplemental Preliminary Amendment filed on June 9, 1999. Claim 24 is directed to "the same as, or for the same or substantially the same subject matter as" claims 3 and 15, respectively, of the Kauffman '476 patent, and were present prior to one year from the date on which this patent issued.

The Kauffman '862 patent issued on November 2, 1999. Claims 26-27 were submitted in the Reply to Office Action filed above on this date, January 14, 2000. Claims 26-27 are directed to "the same as, or for the same or substantially the same subject matter as" claims 1 and 2, respectively, of the Kauffman '862 patent, and are present prior to one year from the date on which this patent issued. [15]

VII. EXPLANATION OF WHY AN INTERFERENCE SHOULD BE DECLARED

As stated in 37 C.F.R. §1.601(i), "[a]n interference is a proceeding instituted in the Patent and Trademark Office before the Board to determine any question of patentability and priority of invention between two or more parties claiming the same patentable invention" [emphasis in original]. According to 37 C.F.R. §1.601(n), "[i]nvention A is the same patentable invention as an invention 'B' when invention 'A' is the same as (35 U.S.C. §102) or

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Not all independent Kauffman claims have been copied, because many are obvious variants of the claims which have been copied, as discussed above in Section III, "Identification of claims of the Kauffman patents which correspond to the proposed Count pursuant to 37 CFR §1.607(a)(3)." However, all independent Kauffman claims have been included in the alternative in the proposed Count to avoid any question of having satisfied the requirements of 37 CFR §1.606, which requires that the Count not be narrower than any patent claim that is designated as corresponding to the Count.

is obvious (35 U.S.C. §103) in view of invention 'B' assuming invention 'B' is prior art with respect to invention 'A'" [emphasis in original].

Claims 1-48 of the Kauffman '323 Patent define the same patentable invention as claims 1-5 of the Kauffman '192 Patent and as claims 1-53 of the Kauffman '483 Patent and as claims 1-46 of the Kauffman '514 Patent and as claims 1-107 of the Kauffman '476 Patent and as claims 1-34 of the Kauffman '862 patent and as claims 3, 4, 6-8 and 11-27 of the instant Horwitz application. Depending on the analysis of the Examiner and the opinion of the Board, claims 1-92 of Pieczenik '363 may also be included. All the claims are essentially directed to or based on methods of searching for biologically active nucleotide sequences from among a randomly or stochastically generated population, on the theory that particular novel sequences capable of predetermined or desired biological functions may be identified. The crux of the invention reflected in all the claims rests on the discovery, which was indeed a "leap of faith" at the time the present invention was made, that randomly generated sequences could perform specific biological functions in the absence of millions of years of evolutionary refinement. While many of the claims in the various Kauffman patents and the corresponding claims submitted in the present application incorporate additional steps beyond the generation and screening of or selecting for randomly generated sequences having a particular function, such steps do not make a patentable difference when considering the state of the art at the time.

Indeed, it was known at the time that polynucleotides could be cloned into expression vectors, and that such vectors could be transformed into and amplified in an appropriate host

cell. It was known that such a host cell could be analyzed, tested or selected based on whether it expressed the protein encoded by or displayed the function provided by the cloned nucleotide sequence. It was known that vector could then be isolated from identified transformed cells and the cloned nucleotide sequence could then be isolated from the vector using standard techniques in the art, i.e., restriction and gel purification. And it was known that such host cells could be used to produce the recombinant protein, which could be purified and used for whatever purpose it was sought, i.e., for vaccine development, as a drug, to raise antibodies, etc. Such manipulations of nucleic acids and standard recombinant techniques do not generally impart a patentable distinction to the novel premise at the time that a completely random population of nucleotides could generate a sequence having a particular biological activity.

Likewise, while many of the claims in the various Kauffman patents and the corresponding claims submitted in the present application incorporate limitations which more precisely define the manner in which nucleotide sequences are generated, or the manner in which nucleotide sequences are screened, or the particular predetermined or desired property of the nucleotide sequence identified, these specific limitations are merely variations of the general concept, and apparent applications of the method, given the state of the art at the time.

Indeed, it was known that nucleotide sequences could be synthesized chemically or by using enzymes like polymerase and terminal transferase. It was known that new nucleotide sequences could be generated by ligating smaller nucleotide sequences together. It was known that DNA could be cleaved with restriction enzymes and re-ligated using DNA ligase following

hybridization of the "sticky ends" of the cleaved DNA. And it was also known that DNA could be ligated in the absence of complementary ends, i.e., blunt-end ligation.

Thus, while there are many claims which have issued in the six Kauffman patents, each merely rephrases the crux of the invention, or adds or specifies particular steps, which would have been apparent to a person skilled in the art when the basic novelty of the invention is taken in view of the state of the art. Furthermore, while the language of the Kauffman claims is slightly different than the instant claims, i.e. "stochastic" instead of "random, without reference to a wild type sequence" each set of claims is based on the same novel premise: that novel nucleotide sequences may be identified in a random population which have or exhibit a desired biological activity.[16]

Therefore, because the Kauffman and Horwitz claims define the same patentable invention, an interference between claims 1-48 of the Kauffman '323 Patent, claims 1-5 of the Kauffman '192 Patent, claims 1-53 of the Kauffman '483 Patent, claims 1-46 of the Kauffman '514 Patent, claims 1-107 of the Kauffman '476 Patent, claims 1-34 of the Kauffman '862 patent and claims 3, 4, 6-8 and 11-25 of the instant Horwitz application should be declared.[17]

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[16] "Random, without reference to a wild type sequence," emphasizes the manner in which the present invention distinguishes over the prior art. Oligonucleotides for the typical mutagenesis experiment of the prior art were synthesized with a bias toward wild type. In contrast, the present invention requires no prior knowledge of structure-function relationships. However, this language does not preclude situations where there is knowledge of a wild type sequence. Rather, it merely indicates that such knowledge is not required.

[17] The Pieczenik '363 patent should not be added to the intereference for the reasons discussed above in Section V.

With regard to the Kauffman applications which are thought to be still pending at the Patent & Trademark Office, while applicants do not have specific knowledge of any claim in such applications, given the fact that all the claims in the six issued Kauffman patents are directed to the same patentable invention as disclosed and claimed in the present application, applicants suspect that any pending Kauffman application should also be included in the interference. Indeed, in view of the many ways in which Kauffman has defined the same invention through the claims of the six issued patents, it is expected that Kauffman will repackage the invention in as many ways as are linguistically possible in any applications which remain pending.

The Examiner is respectfully requested to review any related pending application as to whether such application contains claims which are directed to the same patentable invention as defined by those discussed herein, and determine whether such application or applications should be included in the interference. If necessary, the Examiner is respectfully requested to suggest a claim to applicants corresponding to the claims in any pending application pursuant to 37 CFR 1.605(a) so that all related applications may be included in the interference.

VIII. CONCLUSION

Applicants respectfully request than an interference be declared employing the proposed Count set forth on attached Appendix B between claims 1-48 of the Kauffman '323 Patent, claims 1-5 of the Kauffman '192 Patent, claims 1-53 of the Kauffman '483 Patent, claims 1-46 of the Kauffman '514 Patent, claims 1-107 of the Kauffman '476 Patent, claims 1-34 of the Kauffman '862 patent and claims 3, 4, 6-8 and 11-25 of the instant Horwitz application, all designated as corresponding to the Count. If the Examiner still believes that the Pieczenik '363 patent should also be included as a party, applicants concede and suggest the Count attached in Appendix A in order to advance to interference proceedings, but reserve the right to challenge this inclusion at a later date. In addition, Applicants respectfully request that any pending Kauffman applications containing claims directed to the same patentable invention as defined in the Count be included in the interference, as well as any pertinent Pieczenik applications. Such action is respectfully requested.

Respectfully submitted,

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APPENDIX A[1]
PROPOSED COUNT

A method of identifying a peptide, polypeptide or protein having a binding property to a ligand, comprising:

(a) providing a ligand for detecting said binding property;

(b) synthesizing a diverse population of stochastically generated polynucleotide sequences;

(c) inserting said diverse population of stochastically generated polynucleotide sequences into a population of expression vectors to form a diverse population of expression vectors containing stochastically generated polynucleotide sequences;

(d) expressing in host cells said diverse population of expression vectors containing stochastically generated polynucleotide sequences to produce a diverse population of peptides, polypeptides or proteins; and

(e) screening said diverse population of peptides, polypeptides or proteins with said ligand under conditions which allow binding and detection of one or more peptides, polypeptides or proteins having said predetermined property.

or

An isolated, diverse population of peptides, polypeptides, or proteins comprising greater than about 1×10^5 different stochastic amino acid sequences encoded by stochastic polynucleotide sequences.

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[1]This proposed Count includes the material from the previously proposed Count in Appendix A attached to the Request for Interference filed June 9, 1999, as well as the independent claims from Kauffman 5,976,862 (issued November 2, 1999) in the alternative, as well as the pending claims from the present application in the alternative, which were inadvertently omitted from the previously proposed Count. This Count also includes the independent claims from Pieczenik U.S. Patent 5,866,363 in the alternative should the Examiner decide that Pieczenik should be included in the interference.

or

A method of isolating a polynucleotide sequence encoding a peptide, polypeptide or protein having a predetermined binding property to a ligand, comprising:

(a) providing a ligand for detecting said binding property;

(b) synthesizing a diverse population of stochastically generated polynucleotide sequences;

(c) inserting said diverse population of stochastically generated polynucleotide sequences into a population of expression vectors to form a diverse population of expression vectors containing stochastically generated polynucleotide sequences;

(d) expressing in host cells said diverse population of expression vectors containing stochastically generated polynucleotide sequences to produce a diverse population of peptides, polypeptides or proteins;

(e) screening said diverse population of peptides, polypeptides or proteins with said ligand under conditions which allow binding and detection of one or more peptides, polypeptides or proteins to said ligand; and

(f) isolating the stochastically generated polynucleotide sequence or sequences which encoding said peptides, polypeptides or proteins having said predetermined binding property to said ligand.

or

An isolated, diverse population of polynucleotide sequences which encode a diverse population of ligand binding peptides, polypeptides, or proteins comprising greater than about 1×10^5 different stochastic amino acid sequences encoded by the stochastic polynucleotide sequences.

or

A method of isolating a peptide, polypeptide or protein having a binding property, comprising:

(a) providing a ligand for detecting said binding property;

(b) synthesizing a diverse population of stochastically generated polynucleotide sequences;

(c) inserting said diverse population of stochastically generated polynucleotide sequences into a population of expression vectors to form a diverse population of expression vectors containing stochastically generated polynucleotide sequences;

(d) expressing in host cells said diverse population of expression vectors containing stochastically generated polynucleotide sequences to produce a diverse population of peptides, polypeptides or proteins;

(e) screening said diverse population of peptides, polypeptides or proteins with said ligand under conditions which allow binding and detection of one or more peptides, polypeptides or proteins having said predetermined property;

(f) isolating the stochastically generated polynucleotide sequence or sequences encoding said peptides, polypeptides or proteins having said binding property to said ligand; and

(g) using genetic information from said isolated stochastically generated polynucleotide sequence to produce said peptide, polypeptide or protein having said binding property.

or

A method of producing a diverse population of stochastically generated polynucleotide sequences encoding a diverse population of ligand binding peptides, polypeptides or proteins, comprising:

(a) synthesizing a diverse population of stochastically generated polynucleotide sequences selected from a method consisting of stochastic copolymerization of double stranded oligonucleotides, copolymerization of the four kinds of nucleotide triphoshpates consisting of Adenine, Cytosine, Guanine and Thymine, and chemical synthesis; and

(b) inserting said diverse population of stochastically generated polynucleotide sequences into a population of vectors to form a diverse population of vectors containing stochastically generated polynucleotide sequences.

or

An isolated, diverse population of vectors comprising stochastically generated polynucleotide sequences encoding a diverse population of ligand binding peptides, polypeptides, or proteins comprising greater than about $1x10^5$ different stochastic amino acid sequences.

or

An isolated, diverse population of peptides or polypeptides comprising stochastic amino acid sequences encoded by stochastic polynucleotide sequences of about 300 nucleotides or less in length.

or

An isolated, diverse population of polynucleotides sequences encoding a diverse population of ligand binding peptides or polypeptides comprising stochastic amino acid sequences encoded by stochastic polynucleotide sequences of about 300 nucleotides or less in length.

or

An isolated, diverse population of vectors encoding a diverse population of ligand binding peptides or polypeptides comprising stochastic amino acid sequences encoded by stochastically generated polynucleotide sequences of about 300 nucleotides or less in length.

or

An isolated, diverse population of peptides, polypeptides, or proteins comprising stochastic amino acid sequences produced by a method comprising synthesizing a diverse population of stochastically generated polynucleotide sequences selected from a method consisting of stochastic copolymerization of double stranded oligonucleotides, copolymerization of the four kinds of nucleotide triphosphates consisting of Adenine, Cytosine, Guanine and Thymine, and chemical synthesis; and expressing said stochastically generated polynucleotide sequences.

or

A process for the production of a peptide, polypeptide, or protein having a predetermined property, comprising the steps of:

producing by enzymatic or chemical coupling, stochastically generated polynucleotide sequences;

forming a library of expression vectors containing such stochastically generated polynucleotide sequences;

culturing host cells containing the vectors to produce peptides, polypeptides, or proteins encoded by the stochastically generated polynucleotide sequences;

carrying out screening or selection on such host cells, to identify a peptide, polypeptide, or protein produced by the host cells having the predetermined property;

isolating a stochastically generated polynucleotide sequence which encodes the identified peptide, polypeptide, or protein;

using the isolated sequence to produce the peptide, polypeptide, or protein having the predetermined property.

or

A process for the production of a peptide, polypeptide, or protein having a predetermined property, comprising the steps of:

producing by synthetic polynucleotide coupling, a population of stochastically generated polynucleotide sequences;

forming a library of expression vectors containing said population of stochastically generated polynucleotide sequences;

introducing the vectors into host cells;

culturing the host cells;

carrying out screening or selection on said host cells, to identify a peptide, polypeptide, or protein produced by the host cells having the predetermined property;

isolating a stochastically generated polynucleotide sequence which encodes the identified peptide, polypeptide, or protein;

using the isolated sequence to produce the peptide, polypeptide, or protein having the predetermined property.

or

A process for the production of a peptide, polypeptide, or protein having a predetermined property, comprising the steps of:

producing a population of at least partially stochastic synthetic polynucleotide sequences;

introducing the population of at least partially stochastic polynucleotide sequences into host cells to produce transformed host cells;

cultivating the transformed host cells to produce peptides, polypeptides, or proteins expressed by at least some of the stochastic polynucleotide sequences;

carrying out screening and/or selection methods on said transformed host cells to identify clones producing the peptide, polypeptide, or protein having the predetermined property;

isolating the clones so identified; and

growing the isolated clones in a manner so as to produce the peptide, polypeptide, or protein having the predetermined property.

or

A process for the detection or titration of a ligand using a peptide, polypeptide, or protein having a predetermined property, comprising the steps of:

producing by synthetic polynucleotide coupling, a population of stochastically generated polynucleotide sequences;

forming a library of expression vectors containing said population of stochastically generated polynucleotide sequences;

introducing the vectors into host cells;

culturing the host cells containing the vectors to produce peptides, polypeptides, or proteins encoded by the stochastically generated polynucleotide sequences;

carrying out screening or selection on said host cells, to identify a peptide, polypeptide, or protein produced by the host cells having the predetermined property;

contacting the peptide, polypeptide, or protein with two or more concentrations of a ligand; and

determining the amount of peptide, polypeptide or protein bound at each concentration of ligand.

or

A process for the detection or titration of a ligand using a peptide, polypeptide, or protein having a predetermined property, comprising the steps of:

producing a population of at least partially stochastic synthetic polynucleotide sequences;

introducing the population of at least partially stochastic polynucleotide sequences into host cells to produce transformed host cells;

cultivating the transformed host cells to produce peptides, polypeptides, or proteins expressed by at least some of the stochastic polynucleotide sequences;

carrying out screening and/or selection methods on said transformed host cells to identify clones producing the peptide, polypeptide, or protein having the predetermined property;

contacting the peptide, polypeptide, or protein with two or more concentrations of a ligand; and

determining the amount of peptide, polypeptide or protein bound at each concentration of ligand.

or

A method of identifying a peptide, polypeptide or protein having a predetermined property, comprising:

(a) producing a population of peptides, polypeptides or proteins encoded by stochastic polynucleotide sequences;

(b) screening said population of peptides, polypeptides or proteins for said predetermined property under conditions which allow detection of one or more peptides, polypeptides or proteins having said predetermined property.

or

A method of producing a peptide, polypeptide or protein having a predetermined property, comprising:

(a) producing a population of peptides, polypeptides or proteins encoded by stochastic polynucleotide sequences;

(b) screening said population of peptides, polypeptides or proteins for said predetermined property under conditions which allow detection of one or more peptides, polypeptides or proteins having said predetermined property;

(c) isolating the polynucleotide sequence encoding said one or more peptides, polypeptides or proteins having said predetermined property; and

(d) producing said peptide polypeptide or protein.

or

A method of producing a stochastic polynucleotide population, comprising synthesizing stochastic polynucleotide sequences.

or

A method of producing a desired compound, comprising combining a population of peptides, polypeptides or proteins encoded by stochastic polynucleotide sequences with two or more reactant precursors under conditions favorable for said precursors to react, and incubating said population of peptides, polypeptides or proteins with said reactant precursors for sufficient time so as to allow the catalysis of said desired compound.

or

A method of identifying a population of peptides, polypeptides or proteins which catalyze a sequence of chemical reactions, comprising:

(a) combining a population of peptides, polypeptides or proteins encoded by stochastic polynucleotide sequences with two or more reactant precursors under conditions favorable for said precursors to react;

(b) incubating said population of peptides, polypeptides or proteins with said reactant precursors for sufficient time to allow the catalysis of said sequence of chemical reactions, and

(c) determining the presence or absence of a compound produced by said sequence of chemical reactions, the presence of said compound indicating that said population of peptides, polypeptides or proteins can catalyze said sequence of chemical reactions.

or

A process for the production of an expression vector which comprises at least one stochastic sequence of polynucleotides, comprising the steps of:

providing in an appropriate buffer at least three different sequences of oligonucleotides, said oligonucleotides each comprising at least 7 nucleotide residues;

polymerizing said oligonucleotides to form a stochastic sequence of polynucleotides; and ligating said stochastic sequence of polynucleotides into a linearized expression vector.

or

A process for the production of an expression vector capable of producing a transcription product or a translation product comprising at least one stochastic sequence of polynucleotides, comprising the steps of:

linearizing an expression vector;

reacting said linearized expression vector with terminal transferase enzyme in the presence of desired ratios of deoxynucleotide-triphosphates of guanine, cytosine, thymidine, and adenine to form a stochastic polynucleotide sequence at each 3' extremity of said linearized vector;

hybridizing said stochastic polynucleotide sequence at a 3' extremity of said linearized vector; and

synthesizing a second strand from said 3' ends of said hybridized vector by incubating with polymerase.

or

A process for the production of a library of expression vectors capable of producing a transcription product or a translation product, said vectors comprising at least one stochastic sequence of polynucleotides, comprising the steps of:

producing at least one stochastic sequence of polynucleotides;

ligating said stochastic sequence of polynucleotides into an expression vector;

transforming a competent clone with said ligated expression vector;

culturing said transformed clone;

screening and/or selecting said transformed clone in order to isolate a clone expressing a stochastic polynucleotide leading to the synthesis of a transcription product or a translation product;

isolating said selected or screened transformed clone; and

isolating the expression vector cultured in said selected or screened transformed clone so identified.

or

A method of producing a diverse population of vectors comprising:

(a) synthesizing a diverse population of stochastically generated polynucleotide sequences comprising greater than about 1×10^5 different polynucleotide sequences, said method consisting of stochastic copolymerization of double stranded oligonucleotides, copolymerization of the four kinds of nucleotide triphosphates consisting of adenine, cytosine, guaninie and thymine, and chemical synthesis, and

(b) inserting said diverse population of stochastically generated polynucleotide sequences into a population of vectors to form a diverse population of vectors containing stochastically generated polynucleotide sequences.

or

A method of producing a diverse population of vectors, comprising stochastically copolymerizing a diverse population of vectors containing double stranded polynucleotides so as to produce a new population of vectors containing greater than about 1×10^5 different polynucleotide sequences.

or

A method of producing a diverse populations of vectors, comprising:

(a) obtaining one or more diverse populations of vectors containing diverse sequences of double stranded polynucleotides;

(b) digesting the one or more diverse populations of vectors with a restriction enzyme, and

(c) stochastically copolymerizing the one or more diverse populations of double stranded polynucleotides so as to produce a new population of greater than about 1×10^5 different polynucleotide sequences.

or

A process for the production of a transcription product or a translation product, comprising the steps of:

producing a stochastically-generated polynucleotide sequence;

producing a library of expression vectors comprising said stochastic polynucleotide sequence;

transforming or transfecting a competent clone with said library of expression vectors;

amplifying said transformed or transfected competent clone;

screening and/or selecting said transformed or transfected clone in order to isolate a clone expressing a stochastic polynucleotide sequence capable of synthesizing a transcription product or a translation product having a predetermined property; and

isolating said selected or screened transformed clone;

isolating a stochastically generated polynucleotide sequence which encodes the identified transcription product or translation product using the isolated sequence to produce the transcription product or translation product having the predetermined property.

or

A process for the production of a transcription product or a translation product, comprising the steps of:

producing a diverse population of stochastic polynucleotide sequences;

inserting said stochastic polynucleotide sequences into expression vectors to form a diverse population of expression vectors;

transforming or transfecting competent clones with said diverse population of expression vectors comprising said stochastic polynucleotide sequences;

amplifying said transformed or transfected competent clone;

screening and/or selecting said transformed or transfected clones in order to isolate a clone expressing a stochastic polynucleotide capable of synthesizing a transcription product or a translation product having the predetermined property;

isolating said selected or screened transformed clone;

isolating said stochastic polynucleotide sequence which encodes the identified transcription product or translation product;

using the isolated stochastic polynucleotide sequence so as to produce the transcription product or translation product having the predetermined property.

or

A process for the production of a polynucleotide comprising,

producing in an appropriate buffer a diverse population of stochastic polynucleotide sequences;

inserting said stochastic polynucleotide sequences into vectors to form a diverse population of vectors;

introducing said diverse population of vectors into host cells in a manner to produce a diverse population of transformed host cells;

producing independent clones of the host cells so produced;

screening and/or selecting said independent clones of the host cells to identify host cells comprising a stochastic polynucleotide sequence having at least one desired property; and

isolating said stochastic polynucleotide sequence from the selected or screened clones of host cells.

or

A process for the production of an RNA comprising, producing in an appropriate buffer a diverse population of stochastic polynucleotide sequences;

inserting said stochastic polynucleotide sequences into vectors to form a diverse population of vectors;

introducing said diverse population of vectors into host cells in a manner to produce a diverse population of transformed host cells;

producing independent clones of transformed or transfected host cells;

screening and/or selecting said independent clones of the host cells to identify host cells comprising a stochastic polynucleotide sequence capable of producing RNA having at least one desired property; and

isolating said stochastic polynucleotide sequence from the selected or screened clones of host cells.

or

A method of identifying a polynucleotide having a predetermined property, comprising:

(a) producing a population of polynucleotides comprising greater than about 1×10^5 different stochastic polynucleotide sequences;

(b) screening said population of polynucleotides for said predetermined property under conditions which allow detection of one or more polynucleotides having said predetermined property.

or

A method of identifying a polynucleotide having a binding property to a ligand, comprising:

(a) synthesizing a population of stochastic polynucleotide sequences;

(b) inserting said population of stochastic polynucleotide sequences into a population of vectors to form a population of vectors containing stochastic polynucleotide sequences;

(c) expressing in host cells said population of vectors containing stochastic polynucleotide sequences to produce a diverse population of expressed polynucleotides, and

(d) screening said diverse population of polynucleotides with a ligand under conditions which allow binding and detection one or more polynucleotides having said binding property to said ligand.

or

A method of isolating a polynucleotide having a predetermined property, comprising:

(a) producing a population of polynucleotides comprising greater than 1×10^5 different stochastic polynucleotide sequences;

(b) screening said population of stochastic polynucleotide sequences for said predetermined property under conditions which allow detection of one or more polynucleotides having said predetermined property, and

(c) isolating the one or more polynucleotide sequences having said predetermined property.

or

A method of isolating a polynucleotide having a binding property to a ligand, comprising:

(a) synthesizing a population of stochastic polynucleotide sequences;

(b) inserting said population of stochastic polynucleotide sequences into a population of vectors to form a population of vectors containing stochastic polynucleotide sequences;

(c) expressing in host cells said population of vectors containing stochastic polynucleotide sequences to produce a diverse population of expressed polynucleotides, and

(d) screening said diverse population of polynucleotides with a ligand under conditions which allow binding and detection of one or more polynucleotides to said ligand, and

(e) isolating the stochastic polynucleotide sequence or sequences having said binding property to said ligand.

or

A method of producing a diverse population of polynucleotides, comprising stochastically copolymerizing a population of polynucleotides so as to produce a new population of polynucleotides containing greater than about 1×10^6 different polynucleotide sequences.

or

A method of producing a diverse population of polynucleotides, comprising:

(a) obtaining one or more populations of polynucleotides;

(b) cleaving the one or more populations of polynucleotides, and

(c) stochastically copolymerizing the one or more populations of cleaved polynucleotides so as to produce a new population of greater than about 1×10^5 different polynucleotide sequences.

or

An isolated population of polynucleotides, comprising greater than about 1×10^5 different stochastic polynucleotide sequences.

or

A process for the production of a host cell capable of producing a transcription product or a translation product comprising an expression vector, wherein said expression vector comprises at least one stochastic sequence of polynucleotides comprising the steps of:

providing an appropriate buffer at least three different sequences of oligonucleotides, said oligonucleotides each comprising at least 7 nucleotide residues;

polymerizing said oligonucleotides in a manner to form a stochastic sequence of polynucleotides;

ligating said stochastic sequence of polynucleotides into a linearized expression vector; and

transforming a competent host cell with said ligated expression vector.

or

A process for the production of a host cell capable of producing a transcription product or a translation product comprising an expression vector, wherein said expression vector comprises at least one stochastic sequence of polynucleotides comprising the steps of:

producing a library of expression vectors capable of producing a transcription product or a translation product, said expression vectors comprising at least one stochastic sequence of polynucleotides, said expression vectors being produced by the following steps:

linearizing an expression vector;

reacting said linearized expression vector with terminal transferase enzyme in the presence of desired ratios of deoxynucleotide-triphosphates of guanine, cystosine, thymidine, and adenine to form a stochastic polynucleotide sequence at each 3' extremity of said linearized vector;

hybridizing said stochastic polynucleotide sequence at a 3' extremity of said linearized expression vector;

synthesizing a second strand from said 3' ends of said hybridized expression vector by incubating with polymerase; and

transforming a host cell with said expression vector.

or

A process for the production of a host cell capable of producing a transcription product or a translation product comprising an expression vector, wherein said expression vector comprises at least one stochastic sequence of polynucleotides comprising the steps of:

producing a library of expression vectors capable of producing a transcription product or a translation product, said expression vectors comprising at least one stochastic sequence of polynucleotides;

transforming a host cell with said expression vector;

culturing said transformed host cell;

screening and/or selecting said transformed host cell; and

isolating said selected or screened host cell.

or

A method of producing a diverse population of host cells comprising:

(a) synthesizing a diverse population of stochastically generated polynucleotide sequences comprising greater than about $1x10^5$ different polynucleotide sequences, said method consisting of stochastic copolymerization of double stranded oligonucleotides, copolymerization of the four kinds of nucleotide triphosphates consisting of adenine, cytosine, guanine and thymine, and chemical synthesis, and

(b) inserting said diverse population of stochastically generated polynucleotide sequences into a population of vectors to form a diverse population of vectors containing stochastically generated polynucleotide sequences; and

(c) inserting said diverse population of vectors into host cells.

or

A method of producing a diverse population of host cells, comprising stochastically copolymerizing a diverse population of vectors containing double stranded polynucleotides so as to produce a new population of vectors containing greater than about $1x10^5$ different polynucleotide sequences and inserting said new population of vectors into host cells.

or

A method of producing a diverse populations of host cells, comprising:

(a) obtaining one or more diverse populations of vectors containing diverse sequences of double stranded polynucleotides;

(b) digesting the one or more diverse populations of vectors with a restriction enzyme, and

(c) stochastically copolymerizing the one or more diverse populations of double stranded polynucleotides so as to produce a new population of greater than about $1x10^5$ different polynucleotide sequences; and

(d) inserting said new population of polynucleotides into host cells.

or

A method of identifying a functional nucleotide sequence which provides a desired biological activity comprising:

(a) providing a means for detecting said desired biological activity;

(b) synthesizing a mixed population of random nucleotide sequences by enzymatic or chemical synthesis wherein said population is synthesized without reference to a wild type sequence;

(c) introducing a plurality of the random nucleotide sequences into a population of cloning vectors to obtain a plurality of cloning vectors containing random nucleotide sequences;

(d) introducing said cloning vectors into suitable host cells;

(e) expressing said cloning vectors in said host cells; and

(f) screening said host cells using said means for detecting the desired biological activity under conditions which allow detection of one or more host cells comprising vectors which comprise a functional nucleotide sequence which provides the desired biological activity.

or

A method of isolating a functional nucleotide sequence which provides a desired biological activity comprising:

(a) providing a means for detecting said desired biological activity;

(b) synthesizing a mixed population of random nucleotide sequences by enzymatic or chemical synthesis wherein said population is synthesized without reference to a wild type sequence;

(c) introducing a plurality of said random nucleotide sequences into a population of cloning vectors to obtain a plurality of cloning vectors containing random nucleotide sequences;

(d) introducing said cloning vectors into suitable host cells;

(e) expressing said cloning vectors in said host cells;

(f) screening said host cells using said means for detecting the desired biological activity under conditions which allow detection of one or more host cells comprising vectors which comprise a functional nucleotide sequence which provides the desired biological activity; and

(g) isolating said nucleotide sequence or sequences which provide the desired biological activity.

or

A method of isolating a host cell which comprises a functional nucleotide sequence which produces a desired biological activity comprising:

(a) providing a means for detecting said desired biological activity;

(b) synthesizing a mixed population of random oligonucleotides by enzymatic or chemical synthesis wherein said population is synthesized without reference to a wild type sequence;

(c) introducing a plurality of said random oligonucleotides into a population of cloning vectors to obtain a plurality of cloning vectors containing random oligonucleotides;

(d) introducing said cloning vectors into suitable host cells;

(e) expressing said cloning vectors in said host cells;

(f) screening said host cells to determine whether the inserted oligonucleotide provides the desired biological activity;

(g) isolating said host cells having said oligonucleotide having the desired biological activity.

or

A method of producing a mixed population of random nucleotide sequences in order to identify one or more functional sequences which provide a desired biological activity comprising:

(a) synthesizing a mixed population of random nucleotide sequences in a manner by which the frequency of stop codons in said mixed population is reduced as compared to codons encoding amino acids; and

(b) inserting said mixed population of random nucleotide sequences into a population of cloning vectors to form a mixed population of vectors containing randomly generated sequences.

or

An isolated, mixed population of vectors comprising randomly generated nucleotide sequences encoding a mixed population of amino acid sequences and having a reduced frequency of stop codons as compared to codons encoding amino acids.

or

An isolated, mixed population of random nucleotide sequences comprising a nucleotide sequence providing a desired biological activity produced by a method comprising synthesizing a mixed population of random nucleotide sequences in a manner which biases against stop codons, and introducing a plurality of said randomly generated nucleotide sequences into a population of cloning vectors to form a mixed population of vectors containing randomly generated nucleotide sequences.

or

A method of identifying a functional nucleotide sequence which provides a desired biological activity comprising:

(a) providing a means for detecting said desired biological activity;

(b) synthesizing a mixed population of random nucleotide sequences in a manner by which the frequency of stop codons in said mixed population is reduced as compared to codons encoding amino acids;

(c) introducing a plurality of random nucleotide sequences into a population of cloning vectors to obtain a plurality of cloning vectors containing random nucleotide sequences;

(d) introducing said cloning vectors into suitable host cells;

(e) expressing said cloning vectors in said host cells; and

(f) screening said host cells using said means for detecting the desired biological activity under conditions which allow detection of one or more host cells comprising vectors

which comprise a functional nucleotide sequence which provides the desired biological activity.

or

A method of identifying a peptide, polypeptide or protein having a desired biological activity comprising:

(a) providing a means for detecting said desired biological activity;

(b) synthesizing a mixed population of random nucleotide sequences by enzymatic or chemical synthesis wherein said population is synthesized without reference to a wild type sequence;

(c) introducing a plurality of said random nucleotide sequences into a population of cloning vectors to obtain a plurality of cloning vectors containing random nucleotide sequences;

(d) introducing said cloning vectors into suitable host cells;

(e) expressing said cloning vectors in said host cells to produce a random population of peptides, polypeptides or proteins; and

(f) screening said random population of peptides, polypeptides or proteins with said means for detecting the desired biological activity under conditions which allow detection of one or more peptides, polypeptides or proteins from said random population having the desired biological activity.

or

A method of identifying a peptide, polypeptide or protein that reacts with a substrate:

(a) providing a substrate;

(b) synthesizing a mixed population of random nucleotide sequences by enzymatic or chemical synthesis wherein said population is synthesized without reference to a wild type sequence;

(c) introducing a plurality of said random nucleotide sequences into a population of cloning vectors to obtain a plurality of cloning vectors containing random nucleotide sequences;

(d) introducing said cloning vectors into suitable host cells;

(e) expressing said cloning vectors in said host cells to produce a random population of peptides, polypeptides or proteins; and

(f) screening said random population of peptides, polypeptides or proteins with said substrate under conditions which allow detection of one or more peptides, polypeptides or proteins from said random population that react with said substrate.

or

A process for the production of a peptide or protein having a desired biological activity comprising the steps of:

producing by enzymatic or chemical synthesis a random population of nucleotide sequences wherein said population is produced without reference to a wild type sequence;

forming a library of expression vectors containing the random population of nucleotide sequences;

culturing host cells containing the vectors to produce peptides or proteins encoded by the random population of nucleotide sequences;

carrying out screening or selection on the host cells, to identify a peptide or protein produced by the host cells having the desired biological function;

isolating a randomly synthesized nucleotide sequence which encodes the identified peptide or protein; and

using the isolated sequence to produce the peptide or protein having the desired biological activity.

or

A method of identifying a peptide or protein having a desired biological activity, comprising:

(a) producing a population of peptides or proteins encoded by random nucleotide sequences produced by enzymatic or chemical synthesis wherein said population of nucleotide sequences is produced without reference to a wild type sequence; and

(b) screening said population of peptides or proteins for said desired biological activity under conditions which allow detection of one or more peptides or proteins having said desired biological activity.

or

A method of producing a peptide or protein having a desired biological function, comprising:

(a) producing a population of peptides or proteins encoded by random nucleotide sequences produced by enzymatic or chemical synthesis wherein said population of nucleotide sequences is produced without reference to a wild type sequence;

(b) screening said population of peptides or proteins for said desired biological function under conditions which allow detection of one or more peptides, polypeptides or proteins having said desired biological function;

(c) isolating the nucleotide sequence(s) encoding said one or more peptides or proteins having said desired biological property; and

(d) producing said peptide or protein.

or

A method of producing a random polynucleotide population for use in screening for a desired biological function, comprising adding random nucleotides to an expression vector without reference to a wild type sequence.

or

A method of generating a product of an enzyme-substrate reaction, comprising combining a population of peptides or proteins encoded by random nucleotide sequences, wherein said population of nucleotide sequences is produced without reference to a wild type sequence, with substrate under conditions such that said enzyme-substrate reaction may occur, and incubating said population of peptides or proteins with said substrate such that said product may be detected.

or

A method of identifying a population of peptides or proteins which catalyze an enzyme substrate reaction, comprising:

(a) combining a population of peptides or proteins encoded by random nucleotide sequences, wherein said population of nucleotide sequences is produced without reference to a wild type sequence, with substrate under conditions such that said enzyme-substrate reaction may occur;

(b) incubating said population of peptides or proteins with said enzyme substrate so that a product of said enzyme-substrate reaction may be generated; and

(c) screening for the product of the enzyme-substrate reaction to identify a population of peptides or proteins which catalyze said enzyme-substrate reaction.

or

A process for the production of an expression vector capable of transcribing or translating an open reading frame to produce a desired biological function, said vector comprising a random nucleotide sequence, comprising the steps of:

producing a random population of nucleotide sequences by enzymatic or chemical synthesis wherein said population of nucleotide sequences is produced without reference to a wild type sequence;

ligating said random population of nucleotide sequences into an expression vector to form a library of expression vectors;

transforming suitable host cells with said library of expression vectors;

growing the transformed host cells containing said expression vectors;

screening said transformed host cells in order to identify an expression vector capable of transcribing or translating an open reading frame to produce the desired biological function, or selecting said host cells containing an expression vector capable of transcribing or translating an open reading frame to produce the desired biological function;

isolating the identified or selected transformed host cell; and

isolating the expression vector from said isolated host cell.

or

A method for producing a random population of vectors comprising:

(a) synthesizing a heterogenous population of random nucleotide sequences comprising about a billion or more different nucleotide sequences, said method consisting of random ligation of oligonucleotides or random addition of nucleotide triphosphates without reference to a wild type sequence, and

(b) inserting said heterogenous population of random nucleotide sequences into a population of vectors to form a heterogenous population of vectors containing random nucleotide sequences.

or

A process for the production of a nucleotide sequence comprising,

producing a heterogenous population of random nucleotide sequences by enzymatic or chemical synthesis wherein said population of is produced without reference to a wild type sequence;

inserting said population of random nucleotide sequences into vectors to form a random population of vectors;

introducing said random population of vectors into host cells in a manner to produce a random population of transformed host cells;

growing independent colonies from the transformed host cells;

screening and/or selecting said colonies of the host cells to identify host cells comprising a nucleotide sequence having a desired biological activity; and

isolating said nucleotide sequence from the selected or screened host cells.

or

A method of identifying a nucleotide sequence having a desired biological activity, comprising:

(a) producing a population of nucleotide sequences comprising about a billion or more different random nucleotide sequences by enzymatic or chemical synthesis wherein said population is produced without reference to a wild type sequence;

(b) screening said population of nucleotide sequences for said desired biological activity under conditions which allow detection of nucleotide sequences having said desired biological activity.

or

A method of identifying a functional nucleotide sequence which provides a desired biological activity comprising:

(a) providing a means for detecting said desired biological activity;

(b) forming a population of cloning vectors, each containing a random nucleotide sequence produced by enzymatic or chemical synthesis wherein said random nucleotide sequences are produced without reference to a wild type sequence;

(c) introducing said cloning vectors into suitable host cells;

(d) expressing said cloning vectors in said host cells; and

(e) screening said host cells using said means for detecting the desired biological activity under conditions which allow detection of one or more host cells comprising vectors which comprise a functional nucleotide sequence which provides the desired biological activity.

or

A method of producing a host cell which provides a desired biological activity comprising an expression vector, wherein said expression vector comprises at least one random nucleotide sequence comprising:

(a) synthesizing a mixed population of random nucleotide sequences by enzymatic or chemical synthesis without reference to a wild type sequence;

(b) inserting said mixed population of random nucleotide sequences into a population of cloning vectors to form a mixed population of vectors containing randomly generated sequences; and

(c) transforming a competent host cell with a vector containing a randomly generated sequence.

or

A method of producing a host cell which provides a desired biological activity comprising an expression vector, wherein said expression vector comprises at least one random nucleotide sequence comprising:

(a) synthesizing a mixed population of random single-stranded nucleotide sequences using terminal transferase wherein the frequency of stop codons is reduced in comparison to codons encoding amino acids;

(b) making said single-stranded sequences double-stranded using DNA polymerase;

(c) producing a mixed population of vectors containing said randomly generated sequences; and

(d) transforming a competent host cell with a vector containing a randomly generated sequence.

or

A population of recombinant vectors comprising:

autonomously replicating nucleic acid sequences which nucleic acid sequences comprise a recombinant structural gene, each of the structural genes comprising an insert containing one member of an oligonucleotide population,

said oligonucleotide population comprising oligonucleotides comprising a coding region consisting of a length from about 4 to about 12 nucleotide triplets, said oligonucleotide population encoding a plurality of corresponding random peptide sequences of from about 4 to about 12 L-amino acid residues, and

wherein said recombinant structural genes are expressed upon transfer of said recombinant vectors into *Escherichia coli* host cells, and wherein expression of the recombinant structural genes yields polypeptides, each polypeptide comprising one of said plurality of corresponding random peptide sequences.

or

A population of oligonucleotides comprising double-stranded oligonucleotides comprising coding regions consisting of a length of from about 4 to about 12 nucleotide triplets, said coding regions encoding a plurality of peptide sequences of from about 4 to about

12 L-amino acid residues, said oligonucleotides also comprising 5' and 3' flanking sequences that permit said oligonucleotides to be ligated into a vector,

and wherein in the sum of said peptide sequences represents at least about 10% of all possible peptide sequences of said length.

or

A method of producing a population of epitopic peptide sequences, comprising the steps of:

providing a population of recombinant *E. coli* cells, each of said cells containing at least one member of a recombinant vector population, each member of said vector population comprising substantially identical autonomously replicating nucleic acid sequences, said nucleic acid sequences comprising a recombinant structural gene, each structural gene having inserted therein one member of an oligonucleotide population wherein each member of said oligonucleotide population has a coding region having a length from about 4 to about 12 nucleotide triplets that encodes a corresponding epitopic peptide sequence of from about 4 to about 12 L-amino acid residues, and wherein each member of said oligonucleotide population is contained in said recombinant vector population and wherein the sum of said corresponding epitopic peptide sequences represents substantially all possible peptide sequences of said length; and

culturing said recombinant *E. coli* cells to allow expression of said recombinant structural genes such that said epitopic peptide sequences are accessible to antibody recognition.

or

A population of recombinant vectors comprising:

substantially identical autonomously replicating nucleic acid sequences comprising a recombinant structural gene, each structural gene having inserted therein a member of an

oligonucleotide population, wherein each member of said oligonucleotide population has a coding region having a length from about 4 to about 12 nucleotide triplets that encodes a corresponding peptide sequence of from about 4 to about 12 L-amino acid residues, and wherein the sum of corresponding peptide sequences encoded by said oligonucleotide population represents at least about 10% of all possible peptide sequences of said length,

and wherein each member of said oligonucleotide population is contained in said recombinant vector population; and

wherein the recombinant structural genes are expressed upon transfer of said recombinant vectors into *Escherichia coli* host cells, and wherein expression of said recombinant structural genes yields polypeptides, each polypeptide comprising said corresponding peptide sequence.

or

A method of producing a population of epitopic peptide sequences, comprising the steps of:

providing a population of recombinant *E. coli* cells, each of said cells containing at least one member of a recombinant vector population, each member of said vector population comprising substantially identical autonomously replicating nucleic acid sequences, said nucleic acid sequences comprising a recombinant structural gene, each structural gene having inserted therein one member of an oligonucleotide population wherein each member of said oligonucleotide population has a length from about 4 to about 12 nucleotide triplets that encodes a corresponding epitopic peptide sequence of from about 4 to about 12 L-amino acid residues, and wherein each member of said oligonucleotide population is contained in said recombinant vector population and wherein the sum of said corresponding epitopic peptide sequences represents at least about 10% of all possible peptide sequences of said length; and

culturing said recombinant *E. coli* cells to allow expression of said recombinant structural genes such that said epitopic peptide sequences are accessible to antibody recognition.

or

A population of binding pairs comprising:

a population of peptides, each member of said population having a length of from about 4 to about 12 amino acid residues, wherein said population represents at least about 10 percent of all possible peptide sequences of said length, wherein substantially every member of said peptide population is bound to an antibody.

or

A population of oligonucleotides comprising double stranded oligonucleotides that comprise coding regions consisting of a length of from about 4 to about 12 nucleotide triplets said coding regions encoding a plurality of peptides consisting of random sequences of from about 4 to about 12 L-amino acid residues, said oligonucleotides comprising 5' and 3' flanking sequences that permit said oligonucleotide to be ligated into a vector.

or

A peptide population comprising peptides consisting of random sequences of from about 4 to about 12 amino acid residues.

or

A population of binding pairs comprising:

a peptide population comprising peptides consisting of random sequences of from about 4 to about 12 amino acid residues, wherein substantially every member of said peptide population is bound to an antibody.

or

A method of producing a population of epitopic peptide sequences, comprising:

providing a population of recombinant *Escherichia coli* cells, each of said cells containing at least one member of a recombinant vector population, each member of said vector population comprising autonomously replicating nucleic acid sequences, said nucleic acid sequences comprising a recombinant structural gene, each structural gene containing an insert comprising a member of an oligonucleotide population, said oligonucleotide population comprising oligonucleotides comprising a coding region consisting of a length from about 4 to abut 12 nucleotide triplets, said oligonucleotide population encoding a plurality of epitopic peptides consisting of random sequences of from about 4 to about 12 L-amino acid residues; and

culturing said recombinant *Escherichia coli* cells to allow expression of said recombinant structural genes such that said epitopic peptide sequences are accessible to antibody recognition.

APPENDIX B[1]
PROPOSED COUNT

A method of identifying a peptide, polypeptide or protein having a binding property to a ligand, comprising:

(a) providing a ligand for detecting said binding property;

(b) synthesizing a diverse population of stochastically generated polynucleotide sequences;

(c) inserting said diverse population of stochastically generated polynucleotide sequences into a population of expression vectors to form a diverse population of expression vectors containing stochastically generated polynucleotide sequences;

(d) expressing in host cells said diverse population of expression vectors containing stochastically generated polynucleotide sequences to produce a diverse population of peptides, polypeptides or proteins; and

(e) screening said diverse population of peptides, polypeptides or proteins with said ligand under conditions which allow binding and detection of one or more peptides, polypeptides or proteins having said predetermined property.

or

An isolated, diverse population of peptides, polypeptides, or proteins comprising greater than about 1×10^5 different stochastic amino acid sequences encoded by stochastic polynucleotide sequences.

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[1]This proposed Count includes the material from the previously proposed Count in Appendix A attached to the Request for Interference filed June 9, 1999, as well as the independent claims from Kauffman 5,976,862 (issued November 2, 1999) in the alternative, as well as the pending claims from the present application in the alternative, which were inadvertently omitted from the previously proposed Count. This proposed Count differs from the Count presented in Appendix A in that it does not include the independent claims from Pieczenik U.S. Patent 5,866,363.

or

A method of isolating a polynucleotide sequence encoding a peptide, polypeptide or protein having a predetermined binding property to a ligand, comprising:

(a) providing a ligand for detecting said binding property;

(b) synthesizing a diverse population of stochastically generated polynucleotide sequences;

(c) inserting said diverse population of stochastically generated polynucleotide sequences into a population of expression vectors to form a diverse population of expression vectors containing stochastically generated polynucleotide sequences;

(d) expressing in host cells said diverse population of expression vectors containing stochastically generated polynucleotide sequences to produce a diverse population of peptides, polypeptides or proteins;

(e) screening said diverse population of peptides, polypeptides or proteins with said ligand under conditions which allow binding and detection of one or more peptides, polypeptides or proteins to said ligand; and

(f) isolating the stochastically generated polynucleotide sequence or sequences which encoding said peptides, polypeptides or proteins having said predetermined binding property to said ligand.

or

An isolated, diverse population of polynucleotide sequences which encode a diverse population of ligand binding peptides, polypeptides, or proteins comprising greater than about 1×10^5 different stochastic amino acid sequences encoded by the stochastic polynucleotide sequences.

or

A method of isolating a peptide, polypeptide or protein having a binding property, comprising:

(a) providing a ligand for detecting said binding property;

(b) synthesizing a diverse population of stochastically generated polynucleotide sequences;

(c) inserting said diverse population of stochastically generated polynucleotide sequences into a population of expression vectors to form a diverse population of expression vectors containing stochastically generated polynucleotide sequences;

(d) expressing in host cells said diverse population of expression vectors containing stochastically generated polynucleotide sequences to produce a diverse population of peptides, polypeptides or proteins;

(e) screening said diverse population of peptides, polypeptides or proteins with said ligand under conditions which allow binding and detection of one or more peptides, polypeptides or proteins having said predetermined property;

(f) isolating the stochastically generated polynucleotide sequence or sequences encoding said peptides, polypeptides or proteins having said binding property to said ligand; and

(g) using genetic information from said isolated stochastically generated polynucleotide sequence to produce said peptide, polypeptide or protein having said binding property.

or

A method of producing a diverse population of stochastically generated polynucleotide sequences encoding a diverse population of ligand binding peptides, polypeptides or proteins, comprising:

(a) synthesizing a diverse population of stochastically generated polynucleotide sequences selected from a method consisting of stochastic copolymerization of double stranded oligonucleotides, copolymerization of the four kinds of nucleotide triphoshpates consisting of Adenine, Cytosine, Guanine and Thymine, and chemical synthesis; and

(b) inserting said diverse population of stochastically generated polynucleotide sequences into a population of vectors to form a diverse population of vectors containing stochastically generated polynucleotide sequences.

or

An isolated, diverse population of vectors comprising stochastically generated polynucleotide sequences encoding a diverse population of ligand binding peptides, polypeptides, or proteins comprising greater than about $1x10^5$ different stochastic amino acid sequences.

or

An isolated, diverse population of peptides or polypeptides comprising stochastic amino acid sequences encoded by stochastic polynucleotide sequences of about 300 nucleotides or less in length.

or

An isolated, diverse population of polynucleotides sequences encoding a diverse population of ligand binding peptides or polypeptides comprising stochastic amino acid sequences encoded by stochastic polynucleotide sequences of about 300 nucleotides or less in length.

or

An isolated, diverse population of vectors encoding a diverse population of ligand binding peptides or polypeptides comprising stochastic amino acid sequences encoded by stochastically generated polynucleotide sequences of about 300 nucleotides or less in length.

or

An isolated, diverse population of peptides, polypeptides, or proteins comprising stochastic amino acid sequences produced by a method comprising synthesizing a diverse population of stochastically generated polynucleotide sequences selected from a method consisting of stochastic copolymerization of double stranded oligonucleotides, copolymerization of the four kinds of nucleotide triphosphates consisting of Adenine, Cytosine, Guanine and Thymine, and chemical synthesis; and expressing said stochastically generated polynucleotide sequences.

or

A process for the production of a peptide, polypeptide, or protein having a predetermined property, comprising the steps of:

producing by enzymatic or chemical coupling, stochastically generated polynucleotide sequences;

forming a library of expression vectors containing such stochastically generated polynucleotide sequences;

culturing host cells containing the vectors to produce peptides, polypeptides, or proteins encoded by the stochastically generated polynucleotide sequences;

carrying out screening or selection on such host cells, to identify a peptide, polypeptide, or protein produced by the host cells having the predetermined property;

isolating a stochastically generated polynucleotide sequence which encodes the identified peptide, polypeptide, or protein;

using the isolated sequence to produce the peptide, polypeptide, or protein having the predetermined property.

or

A process for the production of a peptide, polypeptide, or protein having a predetermined property, comprising the steps of:

producing by synthetic polynucleotide coupling, a population of stochastically generated polynucleotide sequences;

forming a library of expression vectors containing said population of stochastically generated polynucleotide sequences;

introducing the vectors into host cells;

culturing the host cells;

carrying out screening or selection on said host cells, to identify a peptide, polypeptide, or protein produced by the host cells having the predetermined property;

isolating a stochastically generated polynucleotide sequence which encodes the identified peptide, polypeptide, or protein;

using the isolated sequence to produce the peptide, polypeptide, or protein having the predetermined property.

or

A process for the production of a peptide, polypeptide, or protein having a predetermined property, comprising the steps of:

producing a population of at least partially stochastic synthetic polynucleotide sequences;

introducing the population of at least partially stochastic polynucleotide sequences into host cells to produce transformed host cells;

cultivating the transformed host cells to produce peptides, polypeptides, or proteins expressed by at least some of the stochastic polynucleotide sequences;

carrying out screening and/or selection methods on said transformed host cells to identify clones producing the peptide, polypeptide, or protein having the predetermined property;

isolating the clones so identified; and

growing the isolated clones in a manner so as to produce the peptide, polypeptide, or protein having the predetermined property.

or

A process for the detection or titration of a ligand using a peptide, polypeptide, or protein having a predetermined property, comprising the steps of:

producing by synthetic polynucleotide coupling, a population of stochastically generated polynucleotide sequences;

forming a library of expression vectors containing said population of stochastically generated polynucleotide sequences;

introducing the vectors into host cells;

culturing the host cells containing the vectors to produce peptides, polypeptides, or proteins encoded by the stochastically generated polynucleotide sequences;

carrying out screening or selection on said host cells, to identify a peptide, polypeptide, or protein produced by the host cells having the predetermined property;

contacting the peptide, polypeptide, or protein with two or more concentrations of a ligand; and

determining the amount of peptide, polypeptide or protein bound at each concentration of ligand.

or

A process for the detection or titration of a ligand using a peptide, polypeptide, or protein having a predetermined property, comprising the steps of:

producing a population of at least partially stochastic synthetic polynucleotide sequences;

introducing the population of at least partially stochastic polynucleotide sequences into host cells to produce transformed host cells;

cultivating the transformed host cells to produce peptides, polypeptides, or proteins expressed by at least some of the stochastic polynucleotide sequences;

carrying out screening and/or selection methods on said transformed host cells to identify clones producing the peptide, polypeptide, or protein having the predetermined property;

contacting the peptide, polypeptide, or protein with two or more concentrations of a ligand; and

determining the amount of peptide, polypeptide or protein bound at each concentration of ligand.

or

A method of identifying a peptide, polypeptide or protein having a predetermined property, comprising:

(a) producing a population of peptides, polypeptides or proteins encoded by stochastic polynucleotide sequences;

(b) screening said population of peptides, polypeptides or proteins for said predetermined property under conditions which allow detection of one or more peptides, polypeptides or proteins having said predetermined property.

or

A method of producing a peptide, polypeptide or protein having a predetermined property, comprising:

(a) producing a population of peptides, polypeptides or proteins encoded by stochastic polynucleotide sequences;

(b) screening said population of peptides, polypeptides or proteins for said predetermined property under conditions which allow detection of one or more peptides, polypeptides or proteins having said predetermined property;

(c) isolating the polynucleotide sequence encoding said one or more peptides, polypeptides or proteins having said predetermined property; and

(d) producing said peptide polypeptide or protein.

or

A method of producing a stochastic polynucleotide population, comprising synthesizing stochastic polynucleotide sequences.

or

A method of producing a desired compound, comprising combining a population of peptides, polypeptides or proteins encoded by stochastic polynucleotide sequences with two or more reactant precursors under conditions favorable for said precursors to react, and incubating said population of peptides, polypeptides or proteins with said reactant precursors for sufficient time so as to allow the catalysis of said desired compound.

or

A method of identifying a population of peptides, polypeptides or proteins which catalyze a sequence of chemical reactions, comprising:

(a) combining a population of peptides, polypeptides or proteins encoded by stochastic polynucleotide sequences with two or more reactant precursors under conditions favorable for said precursors to react;

(b) incubating said population of peptides, polypeptides or proteins with said reactant precursors for sufficient time to allow the catalysis of said sequence of chemical reactions, and

(c) determining the presence or absence of a compound produced by said sequence of chemical reactions, the presence of said compound indicating that said population of peptides, polypeptides or proteins can catalyze said sequence of chemical reactions.

or

A process for the production of an expression vector which comprises at least one stochastic sequence of polynucleotides, comprising the steps of:

providing in an appropriate buffer at least three different sequences of oligonucleotides, said oligonucleotides each comprising at least 7 nucleotide residues;

polymerizing said oligonucleotides to form a stochastic sequence of polynucleotides; and ligating said stochastic sequence of polynucleotides into a linearized expression vector.

or

A process for the production of an expression vector capable of producing a transcription product or a translation product comprising at least one stochastic sequence of polynucleotides, comprising the steps of:

linearizing an expression vector;

reacting said linearized expression vector with terminal transferase enzyme in the presence of desired ratios of deoxynucleotide-triphosphates of guanine, cytosine, thymidine, and adenine to form a stochastic polynucleotide sequence at each 3' extremity of said linearized vector;

hybridizing said stochastic polynucleotide sequence at a 3' extremity of said linearized vector; and

synthesizing a second strand from said 3' ends of said hybridized vector by incubating with polymerase.

or

A process for the production of a library of expression vectors capable of producing a transcription product or a translation product, said vectors comprising at least one stochastic sequence of polynucleotides, comprising the steps of:

producing at least one stochastic sequence of polynucleotides;

ligating said stochastic sequence of polynucleotides into an expression vector;

transforming a competent clone with said ligated expression vector;

culturing said transformed clone;

screening and/or selecting said transformed clone in order to isolate a clone expressing a stochastic polynucleotide leading to the synthesis of a transcription product or a translation product;

isolating said selected or screened transformed clone; and

isolating the expression vector cultured in said selected or screened transformed clone so identified.

or

A method of producing a diverse population of vectors comprising:

(a) synthesizing a diverse population of stochastically generated polynucleotide sequences comprising greater than about 1×10^5 different polynucleotide sequences, said method consisting of stochastic copolymerization of double stranded oligonucleotides,

copolymerization of the four kinds of nucleotide triphosphates consisting of adenine, cytosine, guaninie and thymine, and chemical synthesis, and

(b) inserting said diverse population of stochastically generated polynucleotide sequences into a population of vectors to form a diverse population of vectors containing stochastically generated polynucleotide sequences.

or

A method of producing a diverse population of vectors, comprising stochastically copolymerizing a diverse population of vectors containing double stranded polynucleotides so as to produce a new population of vectors containing greater than about 1×10^5 different polynucleotide sequences.

or

A method of producing a diverse populations of vectors, comprising:

(a) obtaining one or more diverse populations of vectors containing diverse sequences of double stranded polynucleotides;

(b) digesting the one or more diverse populations of vectors with a restriction enzyme, and

(c) stochastically copolymerizing the one or more diverse populations of double stranded polynucleotides so as to produce a new population of greater than about 1×10^5 different polynucleotide sequences.

or

A process for the production of a transcription product or a translation product, comprising the steps of:

producing a stochastically-generated polynucleotide sequence;

producing a library of expression vectors comprising said stochastic polynucleotide sequence;

transforming or transfecting a competent clone with said library of expression vectors;

amplifying said transformed or transfected competent clone;

screening and/or selecting said transformed or transfected clone in order to isolate a clone expressing a stochastic polynucleotide sequence capable of synthesizing a transcription product or a translation product having a predetermined property; and

isolating said selected or screened transformed clone;

isolating a stochastically generated polynucleotide sequence which encodes the identified transcription product or translation product using the isolated sequence to produce the transcription product or translation product having the predetermined property.

or

A process for the production of a transcription product or a translation product, comprising the steps of:

producing a diverse population of stochastic polynucleotide sequences;

inserting said stochastic polynucleotide sequences into expression vectors to form a diverse population of expression vectors;

transforming or transfecting competent clones with said diverse population of expression vectors comprising said stochastic polynucleotide sequences;

amplifying said transformed or transfected competent clone;

screening and/or selecting said transformed or transfected clones in order to isolate a clone expressing a stochastic polynucleotide capable of synthesizing a transcription product or a translation product having the predetermined property;

isolating said selected or screened transformed clone;

isolating said stochastic polynucleotide sequence which encodes the identified transcription product or translation product;

using the isolated stochastic polynucleotide sequence so as to produce the transcription product or translation product having the predetermined property.

or

A process for the production of a polynucleotide comprising,

producing in an appropriate buffer a diverse population of stochastic polynucleotide sequences;

inserting said stochastic polynucleotide sequences into vectors to form a diverse population of vectors;

introducing said diverse population of vectors into host cells in a manner to produce a diverse population of transformed host cells;

producing independent clones of the host cells so produced;

screening and/or selecting said independent clones of the host cells to identify host cells comprising a stochastic polynucleotide sequence having at least one desired property; and

isolating said stochastic polynucleotide sequence from the selected or screened clones of host cells.

or

A process for the production of an RNA comprising, producing in an appropriate buffer a diverse population of stochastic polynucleotide sequences;

inserting said stochastic polynucleotide sequences into vectors to form a diverse population of vectors;

introducing said diverse population of vectors into host cells in a manner to produce a diverse population of transformed host cells;

producing independent clones of transformed or transfected host cells;

screening and/or selecting said independent clones of the host cells to identify host cells comprising a stochastic polynucleotide sequence capable of producing RNA having at least one desired property; and

isolating said stochastic polynucleotide sequence from the selected or screened clones of host cells.

or

A method of identifying a polynucleotide having a predetermined property, comprising:

(a) producing a population of polynucleotides comprising greater than about 1×10^5 different stochastic polynucleotide sequences;

(b) screening said population of polynucleotides for said predetermined property under conditions which allow detection of one or more polynucleotides having said predetermined property.

or

A method of identifying a polynucleotide having a binding property to a ligand, comprising:

(a) synthesizing a population of stochastic polynucleotide sequences;

(b) inserting said population of stochastic polynucleotide sequences into a population of vectors to form a population of vectors containing stochastic polynucleotide sequences;

(c) expressing in host cells said population of vectors containing stochastic polynucleotide sequences to produce a diverse population of expressed polynucleotides, and

(d) screening said diverse population of polynucleotides with a ligand under conditions which allow binding and detection one or more polynucleotides having said binding property to said ligand.

or

A method of isolating a polynucleotide having a predetermined property, comprising:

(a) producing a population of polynucleotides comprising greater than 1 x 10^5 different stochastic polynucleotide sequences;

(b) screening said population of stochastic polynucleotide sequences for said predetermined property under conditions which allow detection of one or more polynucleotides having said predetermined property, and

(c) isolating the one or more polynucleotide sequences having said predetermined property.

or

A method of isolating a polynucleotide having a binding property to a ligand, comprising:

(a) synthesizing a population of stochastic polynucleotide sequences;

(b) inserting said population of stochastic polynucleotide sequences into a population of vectors to form a population of vectors containing stochastic polynucleotide sequences;

(c) expressing in host cells said population of vectors containing stochastic polynucleotide sequences to produce a diverse population of expressed polynucleotides, and

(d) screening said diverse population of polynucleotides with a ligand under conditions which allow binding and detection of one or more polynucleotides to said ligand, and

(e) isolating the stochastic polynucleotide sequence or sequences having said binding property to said ligand.

or

A method of producing a diverse population of polynucleotides, comprising stochastically copolymerizing a population of polynucleotides so as to produce a new population of polynucleotides containing greater than about 1×10^6 different polynucleotide sequences.

or

A method of producing a diverse population of polynucleotides, comprising:

(a) obtaining one or more populations of polynucleotides;

(b) cleaving the one or more populations of polynucleotides, and

(c) stochastically copolymerizing the one or more populations of cleaved polynucleotides so as to produce a new population of greater than about 1×10^5 different polynucleotide sequences.

or

An isolated population of polynucleotides, comprising greater than about 1×10^5 different stochastic polynucleotide sequences.

or

A process for the production of a host cell capable of producing a transcription product or a translation product comprising an expression vector, wherein said expression vector comprises at least one stochastic sequence of polynucleotides comprising the steps of:

producing a library of expression vectors capable of producing a transcription product or a translation product, said expression vectors comprising at least one stochastic sequence of polynucleotides, said expression vectors being produced by the following steps:

providing in an appropriate buffer at least three different sequences of oligonucleotides, said oligonucleotides each comprising at least 7 nucleotide residues;

polymerizing said oligonucleotides in a manner to form a stochastic sequence of polynucleotides;

ligating said stochastic sequence of polynucleotides into a linearized expression vector; and

transforming a competent host cell with said ligated expression vector.

or

A process for the production of a host cell capable of producing a transcription product or a translation product comprising an expression vector, wherein said expression vector comprises at least one stochastic sequence of polynucleotides comprising the steps of:

producing a library of expression vectors capable of producing a transcription product or a translation product, said expression vectors comprising at least one stochastic sequence of polynucleotides, said expression vectors being produced by the following steps:

linearizing an expression vector;

reacting said linearized expression vector with terminal transferase enzyme in the presence of desired ratios of deoxynucleotide-triphosphates of guanine, cystosine, thymidine, and adenine to form a stochastic polynucleotide sequence at each 3' extremity of said linearized vector;

hybridizing said stochastic polynucleotide sequence at a 3' extremity of said linearized expression vector;

synthesizing a second strand from said 3' ends of said hybridized expression vector by incubating with polymerase; and

transforming a host cell with said expression vector.

or

A process for the production of a host cell capable of producing a transcription product or a translation product comprising an expression vector, wherein said expression vector comprises at least one stochastic sequence of polynucleotides comprising the steps of:

producing a library of expression vectors capable of producing a transcription product or a translation product, said expression vectors comprising at least one stochastic sequence of polynucleotides;

transforming a host cell with said expression vector;

culturing said transformed host cell;

screening and/or selecting said transformed host cell; and

isolating said selected or screened host cell.

or

A method of producing a diverse population of host cells comprising:

(a) synthesizing a diverse population of stochastically generated polynucleotide sequences comprising greater than about $1x10^5$ different polynucleotide sequences, said method consisting of stochastic copolymerization of double stranded oligonucleotides, copolymerization of the four kinds of nucleotide triphosphates consisting of adenine, cytosine, guanine and thymine, and chemical synthesis, and

(b) inserting said diverse population of stochastically generated polynucleotide sequences into a population of vectors to form a diverse population of vectors containing stochastically generated polynucleotide sequences; and

(c) inserting said diverse population of vectors into host cells.

or

A method of producing a diverse population of host cells, comprising stochastically copolymerizing a diverse population of vectors containing double stranded polynucleotides so

as to produce a new population of vectors containing greater than about $1x10^5$ different polynucleotide sequences and inserting said new population of vectors into host cells.

or

A method of producing a diverse populations of host cells, comprising:

(a) obtaining one or more diverse populations of vectors containing diverse sequences of double stranded polynucleotides;

(b) digesting the one or more diverse populations of vectors with a restriction enzyme, and

(c) stochastically copolymerizing the one or more diverse populations of double stranded polynucleotides so as to produce a new population of greater than about $1x10^5$ different polynucleotide sequences; and

(d) inserting said new population of polynucleotides into host cells.

or

A method of identifying a functional nucleotide sequence which provides a desired biological activity comprising:

(a) providing a means for detecting said desired biological activity;

(b) synthesizing a mixed population of random nucleotide sequences by enzymatic or chemical synthesis wherein said population is synthesized without reference to a wild type sequence;

(c) introducing a plurality of the random nucleotide sequences into a population of cloning vectors to obtain a plurality of cloning vectors containing random nucleotide sequences;

(d) introducing said cloning vectors into suitable host cells;

(e) expressing said cloning vectors in said host cells; and

(f) screening said host cells using said means for detecting the desired biological activity under conditions which allow detection of one or more host cells comprising vectors which comprise a functional nucleotide sequence which provides the desired biological activity.

or

A method of isolating a functional nucleotide sequence which provides a desired biological activity comprising:

(a) providing a means for detecting said desired biological activity;

(b) synthesizing a mixed population of random nucleotide sequences by enzymatic or chemical synthesis wherein said population is synthesized without reference to a wild type sequence;

(c) introducing a plurality of said random nucleotide sequences into a population of cloning vectors to obtain a plurality of cloning vectors containing random nucleotide sequences;

(d) introducing said cloning vectors into suitable host cells;

(e) expressing said cloning vectors in said host cells;

(f) screening said host cells using said means for detecting the desired biological activity under conditions which allow detection of one or more host cells comprising vectors which comprise a functional nucleotide sequence which provides the desired biological activity; and

(g) isolating said nucleotide sequence or sequences which provide the desired biological activity.

or

A method of isolating a host cell which comprises a functional nucleotide sequence which produces a desired biological activity comprising:

(a) providing a means for detecting said desired biological activity;

(b) synthesizing a mixed population of random oligonucleotides by enzymatic or chemical synthesis wherein said population is synthesized without reference to a wild type sequence;

(c) introducing a plurality of said random oligonucleotides into a population of cloning vectors to obtain a plurality of cloning vectors containing random oligonucleotides;

(d) introducing said cloning vectors into suitable host cells;

(e) expressing said cloning vectors in said host cells;

(f) screening said host cells to determine whether the inserted oligonucleotide provides the desired biological activity;

(g) isolating said host cells having said oligonucleotide having the desired biological activity.

or

A method of producing a mixed population of random nucleotide sequences in order to identify one or more functional sequences which provide a desired biological activity comprising:

(a) synthesizing a mixed population of random nucleotide sequences in a manner by which the frequency of stop codons in said mixed population is reduced as compared to codons encoding amino acids; and

(b) inserting said mixed population of random nucleotide sequences into a population of cloning vectors to form a mixed population of vectors containing randomly generated sequences.

or

An isolated, mixed population of vectors comprising randomly generated nucleotide sequences encoding a mixed population of amino acid sequences and having a reduced frequency of stop codons as compared to codons encoding amino acids.

or

An isolated, mixed population of random nucleotide sequences comprising a nucleotide sequence providing a desired biological activity produced by a method comprising synthesizing a mixed population of random nucleotide sequences in a manner which biases against stop codons, and introducing a plurality of said randomly generated nucleotide sequences into a population of cloning vectors to form a mixed population of vectors containing randomly generated nucleotide sequences.

or

A method of identifying a functional nucleotide sequence which provides a desired biological activity comprising:

(a) providing a means for detecting said desired biological activity;

(b) synthesizing a mixed population of random nucleotide sequences in a manner by which the frequency of stop codons in said mixed population is reduced as compared to codons encoding amino acids;

(c) introducing a plurality of random nucleotide sequences into a population of cloning vectors to obtain a plurality of cloning vectors containing random nucleotide sequences;

(d) introducing said cloning vectors into suitable host cells;

(e) expressing said cloning vectors in said host cells; and

(f) screening said host cells using said means for detecting the desired biological activity under conditions which allow detection of one or more host cells comprising vectors

which comprise a functional nucleotide sequence which provides the desired biological activity.

or

A method of identifying a peptide, polypeptide or protein having a desired biological activity comprising:

(a) providing a means for detecting said desired biological activity;

(b) synthesizing a mixed population of random nucleotide sequences by enzymatic or chemical synthesis wherein said population is synthesized without reference to a wild type sequence;

(c) introducing a plurality of said random nucleotide sequences into a population of cloning vectors to obtain a plurality of cloning vectors containing random nucleotide sequences;

(d) introducing said cloning vectors into suitable host cells;

(e) expressing said cloning vectors in said host cells to produce a random population of peptides, polypeptides or proteins; and

(f) screening said random population of peptides, polypeptides or proteins with said means for detecting the desired biological activity under conditions which allow detection of one or more peptides, polypeptides or proteins from said random population having the desired biological activity.

or

A method of identifying a peptide, polypeptide or protein that reacts with a substrate:

(a) providing a substrate;

(b) synthesizing a mixed population of random nucleotide sequences by enzymatic or chemical synthesis wherein said population is synthesized without reference to a wild type sequence;

(c) introducing a plurality of said random nucleotide sequences into a population of cloning vectors to obtain a plurality of cloning vectors containing random nucleotide sequences;

(d) introducing said cloning vectors into suitable host cells;

(e) expressing said cloning vectors in said host cells to produce a random population of peptides, polypeptides or proteins; and

(f) screening said random population of peptides, polypeptides or proteins with said substrate under conditions which allow detection of one or more peptides, polypeptides or proteins from said random population that react with said substrate.

or

A process for the production of a peptide or protein having a desired biological activity comprising the steps of:

producing by enzymatic or chemical synthesis a random population of nucleotide sequences wherein said population is produced without reference to a wild type sequence;

forming a library of expression vectors containing the random population of nucleotide sequences;

culturing host cells containing the vectors to produce peptides or proteins encoded by the random population of nucleotide sequences;

carrying out screening or selection on the host cells, to identify a peptide or protein produced by the host cells having the desired biological function;

isolating a randomly synthesized nucleotide sequence which encodes the identified peptide or protein; and

using the isolated sequence to produce the peptide or protein having the desired biological activity.

or

A method of identifying a peptide or protein having a desired biological activity, comprising:

(a) producing a population of peptides or proteins encoded by random nucleotide sequences produced by enzymatic or chemical synthesis wherein said population of nucleotide sequences is produced without reference to a wild type sequence; and

(b) screening said population of peptides or proteins for said desired biological activity under conditions which allow detection of one or more peptides or proteins having said desired biological activity.

or

A method of producing a peptide or protein having a desired biological function, comprising:

(a) producing a population of peptides or proteins encoded by random nucleotide sequences produced by enzymatic or chemical synthesis wherein said population of nucleotide sequences is produced without reference to a wild type sequence;

(b) screening said population of peptides or proteins for said desired biological function under conditions which allow detection of one or more peptides, polypeptides or proteins having said desired biological function;

(c) isolating the nucleotide sequence(s) encoding said one or more peptides or proteins having said desired biological property; and

(d) producing said peptide or protein.

or

A method of producing a random polynucleotide population for use in screening for a desired biological function, comprising adding random nucleotides to an expression vector without reference to a wild type sequence.

or

A method of generating a product of an enzyme-substrate reaction, comprising combining a population of peptides or proteins encoded by random nucleotide sequences, wherein said population of nucleotide sequences is produced without reference to a wild type sequence, with substrate under conditions such that said enzyme-substrate reaction may occur, and incubating said population of peptides or proteins with said substrate such that said product may be detected.

or

A method of identifying a population of peptides or proteins which catalyze an enzyme substrate reaction, comprising:

(a) combining a population of peptides or proteins encoded by random nucleotide sequences, wherein said population of nucleotide sequences is produced without reference to a wild type sequence, with substrate under conditions such that said enzyme-substrate reaction may occur;

(b) incubating said population of peptides or proteins with said enzyme substrate so that a product of said enzyme-substrate reaction may be generated; and

(c) screening for the product of the enzyme-substrate reaction to identify a population of peptides or proteins which catalyze said enzyme-substrate reaction.

or

A process for the production of an expression vector capable of transcribing or translating an open reading frame to produce a desired biological function, said vector comprising a random nucleotide sequence, comprising the steps of:

producing a random population of nucleotide sequences by enzymatic or chemical synthesis wherein said population of nucleotide sequences is produced without reference to a wild type sequence;

ligating said random population of nucleotide sequences into an expression vector to form a library of expression vectors;

transforming suitable host cells with said library of expression vectors;

growing the transformed host cells containing said expression vectors;

screening said transformed host cells in order to identify an expression vector capable of transcribing or translating an open reading frame to produce the desired biological function, or selecting said host cells containing an expression vector capable of transcribing or translating an open reading frame to produce the desired biological function;

isolating the identified or selected transformed host cell; and

isolating the expression vector from said isolated host cell.

or

A method for producing a random population of vectors comprising:

(a) synthesizing a heterogenous population of random nucleotide sequences comprising about a billion or more different nucleotide sequences, said method consisting of random ligation of oligonucleotides or random addition of nucleotide triphosphates without reference to a wild type sequence, and

(b) inserting said heterogenous population of random nucleotide sequences into a population of vectors to form a heterogenous population of vectors containing random nucleotide sequences.

or

A process for the production of a nucleotide sequence comprising,

producing a heterogenous population of random nucleotide sequences by enzymatic or chemical synthesis wherein said population of is produced without reference to a wild type sequence;

inserting said population of random nucleotide sequences into vectors to form a random population of vectors;

introducing said random population of vectors into host cells in a manner to produce a random population of transformed host cells;

growing independent colonies from the transformed host cells;

screening and/or selecting said colonies of the host cells to identify host cells comprising a nucleotide sequence having a desired biological activity; and

isolating said nucleotide sequence from the selected or screened host cells.

or

A method of identifying a nucleotide sequence having a desired biological activity, comprising:

(a) producing a population of nucleotide sequences comprising about a billion or more different random nucleotide sequences by enzymatic or chemical synthesis wherein said population is produced without reference to a wild type sequence;

(b) screening said population of nucleotide sequences for said desired biological activity under conditions which allow detection of nucleotide sequences having said desired biological activity.

or

A method of identifying a functional nucleotide sequence which provides a desired biological activity comprising:

(a) providing a means for detecting said desired biological activity;

(b) forming a population of cloning vectors, each containing a random nucleotide sequence produced by enzymatic or chemical synthesis wherein said random nucleotide sequences are produced without reference to a wild type sequence;

(c) introducing said cloning vectors into suitable host cells;

(d) expressing said cloning vectors in said host cells; and

(e) screening said host cells using said means for detecting the desired biological activity under conditions which allow detection of one or more host cells comprising vectors which comprise a functional nucleotide sequence which provides the desired biological activity.

or

A method of producing a host cell which provides a desired biological activity comprising an expression vector, wherein said expression vector comprises at least one random nucleotide sequence comprising:

(a) synthesizing a mixed population of random nucleotide sequences by enzymatic or chemical synthesis without reference to a wild type sequence;

(b) inserting said mixed population of random nucleotide sequences into a population of cloning vectors to form a mixed population of vectors containing randomly generated sequences; and

(c) transforming a competent host cell with a vector containing a randomly generated sequence.

or

A method of producing a host cell which provides a desired biological activity comprising an expression vector, wherein said expression vector comprises at least one random nucleotide sequence comprising:

(a) synthesizing a mixed population of random single-stranded nucleotide sequences using terminal transferase wherein the frequency of stop codons is reduced in comparison to codons encoding amino acids;

(b) making said single-stranded sequences double-stranded using DNA polymerase;

(c) producing a mixed population of vectors containing said randomly generated sequences; and

(d) transforming a competent host cell with a vector containing a randomly generated sequence.

APPENDIX C

APPLICATION OF HORWITZ CLAIMS 26 AND 27 TO THE DISCLOSURE OF THE HORWITZ APPLICATIONS[18,19]

26. A method of producing a host cell which provides a desired biological activity comprising an expression vector, wherein said expression vector comprises at least one random nucleotide sequence comprising:	Page 5, lines 28-29 (page 5, lines 11-13) Paragraph bridging pages 6-7 (page 7, lines 20-28)
a. synthesizing a mixed population of random nucleotide sequences by enzymatic or chemical synthesis without reference to a wild type sequence;	Page 25, lines 30-32 (page 24, lines 28-30)
b. inserting said mixed population of random nucleotide sequences into a population of cloning vectors to form a mixed population of vectors containing randomly generated sequences; and	Page 4, line 14; page 5, lines 1-3 (page 4, lines 7-8)
c. transforming a competent host cell with a vector containing a randomly generated sequence.	Page 4, lines 12-14 (page 3, .lines 18-19)
27. A method of producing a host cell which provides a desired biological activity comprising an expression vector, wherein said expression vector comprises at least one random nucleotide sequence comprising:	See above for claim 26
a. synthesizing a mixed population of random single-stranded nucleotide sequences using terminal transferase	Page 25, lines 30-35 (page 24, lines 28-32)

The support provided for the Horwitz claims corresponding to the proposed Count is merely exemplary and is not meant to imply that additional support cannot be found in the Horwitz specification and claims as originally filed. Corresponding exemplary support in parent application Serial No. 06/887,070, filed July 17, 1986, is set forth in parentheses.

For steps, phrases or words in claims which are used more than once, exemplary support may be shown by referring to a previous claim by the phrase "see above."

wherein the frequency of stop codons is reduced in comparison to codons encoding amino acids;

b. making said single-stranded sequences double-stranded using DNA polymerase;

c. producing a mixed population of vectors containing said randomly generated sequences; and

d. transforming a competent host cell with a vector containing a randomly generated sequence.

Page 26, lines 23-27
(page 25, lines 20-24)

Page 26, lines 5-7
(page 25, lines 2-4)

Page 26, line 10
(page 26, line 7)